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BENIGN CYSTS OF THE ADRENAL GLAND: A CASE REPORT

DEAN PARKER

Benign cysts of the adrenal gland are rare. Prior to 1920, fourteen cases were reported and only five additional cases have been reported in the American literature since then. The first case was cited by Greiselius in 1670.[1] Terrier and Lecene published their case and reviewed nine others reported up to 1906.[2] They also classified adrenal cysts: 1) parasitic, 2) true glandular retention cysts, 3) cystic adenomas, 4) serous or lymphangiomatous cysts and 5) pseudocysts (hemorrhagic cysts). Only 2 cases reported, that of Levinson and this case, were diagnosed prior to surgery.

The etiology of adrenal cysts is somewhat confusing and only a little clarity is gained from the review of literature. Major and Black[3] reported a case of bilateral adrenal cysts which appeared to arise from dilated capillaries or sinusoids between columns of adrenal cells. The cases of Oberndorfer[4] and one by de Vecchi[5] appeared to arise from lymphangiectasia, as did the most recent case in the literature, that of Zuckner.[6] Henchen[7] recorded a hemorrhagic cyst of the adrenal while Sick[8] reported a ciliated cyst which must have developed on the basis of displacement of tissue from the urogenital anlage. Stoerk,[9] and later Nowicki,[10] both expressed doubts as to the existence of true epithelial cysts. This seems logical since there is no tendency to acini formation in the cells of the adrenal gland. Reimann and Guyton[11] believe that most cysts may be classified etiologically as ectasia of pre-existing vessels or lymphatics, or cystic degeneration of hematomas, or adenomas and cites cases reported by Robson and Zimmerman[12] and Iglitsyn[13] in support of this view. Parasitic cysts of the adrenal gland occur but rarely as shown by Barnett,[14] who in a review of 1,617 cases with echinococcus cysts found the adrenal involved in 0.5 per cent of the cases.

Hemorrhagic disease of the adrenal gland is not an uncommon finding at necropsy. It is seen in the newborn associated with certain categories of anoxia. It is seen as a toxic manifestation in meningococcus infections such as the Waterhouse-Fredricksen syndrome. More rarely it is seen in cases of profound

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 27, 1951.

[1] Greiselius, cited by Doran, A. H. G.: Brit. Med. J., 1: 1558, 1908.

[2] Terrier and Lecene, cited by Zuckner, J.: A. M. A. Arch. Path., 50: 468–474, 1950.

[3] Major, R. H. and Black, D. R.: Am. J. Med. Sc., 156: 469, 1918.

[4] Oberndorfer, cited by Zuckner, J.: A. M. A. Arch. Path., 50: 468–474, 1950.

[5] deVecchi, cited by Zuckner, J., Major, R. H. and Black, D. R.: A. M. A. Arch. Path., 50: 468–474, 1950.

[6] Zuckner, J.: A. M. A. Arch. Path., 50: 468–474, 1950.

[7] Henchen, cited by Major, R. H. and Black, D. R.: Am. J. Med. Sc., 156: 469, 1918.

[8] Sick, cited by Major, R. H. and Black, D. R.: Am. J. Med. Sc., 156: 469, 1918.

[9] Stoerk, cited by Major, R. H. and Black, D. R.: Am. J. Med. Sc., 156: 469, 1918. Also by Zuckner, J.: A. M. A. Arch. Path., 50: 468–474, 1950.

[10] Nowicki, cited by Major, R. H. and Black, D. R.: Am. J. Med. Sc., 156: 469, 1918. Also by Zuckner, J.: A. M. A. Arch. Path., 50: 468–474, 1950.

[11] Reimann, D. L. and Guyton, W. L.: Am. J. Path., 23: 479, 1947.

[12] Robson, S. H. and Zimmerman, E. F.: Arch. Path., 26: 869, 1938.

[13] Iglitsyn, cited by Reimann, D. L. and Guyton, W. L.: Am. J. Path., 23: 479, 1947.

[14] Barnett, cited by Levison, P.: Endocrinology, 17: 372, 1933.

An excretory urogram showed a round, well circumscribed mass below the diaphragm, above the right kidney which displaced the upper pole of the right kidney downward and laterally, so that the kidney lay in a horizontal rather than a vertical plane. The calyces, renal pelvis and ureter on the right side were otherwise normal. The left pyelogram was entirely normal. See figure 1.

On hospital admission the systolic blood pressure was 150, and the diastolic 90. A roentgenogram of the chest was normal. A renal study with retrograde pyelograms added no information to that obtained from the excretory urographic series. The 24 hour urinary excretion of the 17-ketosteroids was 17 mg. per cent. The blood pressure response to histamine and dibenamine was normal and showed no evidence of an epinephrine-producing tumor of the adrenal gland. Impression: Benign cyst of the right adrenal gland.

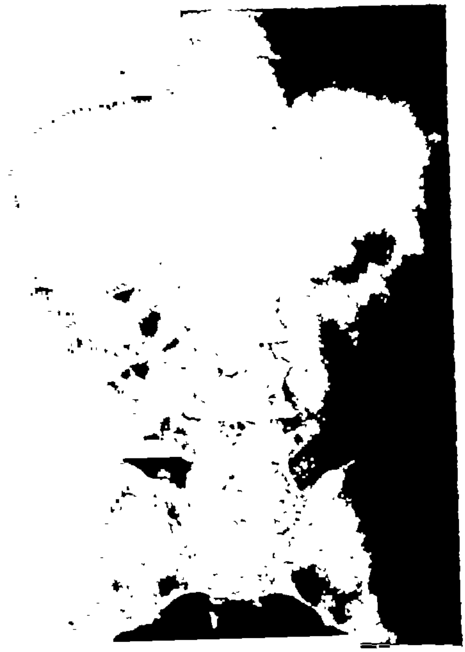

FIG. 1. Excretory urogram showing subdiaphragmatic mass on right, displacing upper pole of kidney.

Operation: With the patient in the right kidney position, a transthoracic approach was made through the right chest by removal of the tenth rib. The fibers of the diaphragm were incised radially from the tendinous portion. A large cyst of the right adrenal gland was easily dissected free from the upper pole of the right kidney down to its vascular pedicle which was really that of the right adrenal gland. The cyst was not attached to the upper pole of the kidney nor to its capsule, but the upper pole of the kidney was concavely indented by the downward pressure of the mass. The wound was closed in layers without drains or water seal by interrupted cotton technique. The skin edges were approximated with interrupted cotton sutures.

The gross specimen consisted of a mass which was almost round. It measured

representing spaces from which cholesterol crystals have been dissolved. Within this area there are some areas of calcific deposit. Also seen within this material here and there are a few large cells which show a vacuolated cytoplasm and which may represent degenerated adrenal cells or possibly phagocytic cells with vacuolization." Microscopic diagnosis: Adrenal cyst. See figure 3.

The patient had some difficulty in coughing and bronchial aspiration was done on the first postoperative day. A chest aspiration was done on the second postoperative day. The highest elevation of temperature was 100F and he was discharged on the eighth postoperative day. He was last seen 6 months later entirely asymptomatic.

SUMMARY

A case of benign cyst of the adrenal gland has been reported and the literature has been reviewed with an attempt to classify such cysts according to etiological factors. A preoperative diagnosis was made primarily on the basis of the radiographic peculiarity of the lesion in question. This case emphasizes the advantages in the transthoracic approach and its use in upper pole renal or adrenal disease.

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Examination of kidneys removed from patients with hypertension indicates that chronic renal infection is an important etiologic factor. The infection must be of long standing and must cause widespread cicatricial changes in the renal tissue. Acute renal infections such as acute pyelonephritis, renal carbuncle and perinephric abscess seldom are immediate causes of hypertension. Subsequent extensive infection, with fibrosis and renal atrophy, however, may be accompanied by hypertension. Although it might be expected that hypertension would be commonly found along with chronic bilateral pyelonephritis, this is not the case until the terminal stages of the disease. The intrarenal circulation usually is involved only secondarily in the early stages and sufficient normal renal tissue remains to take care of renal function for many years. The blood pressure of most patients with chronic bilateral pyelonephritis, as observed by urologists, is within normal limits. The high incidence of hypertension (65 per cent) reported in cases of chronic pyelonephritis in which necropsy is done, does not represent the usual clinical experience.

The unilateral renal lesions which most frequently are encountered in cases of hypertension, and which are followed by the best results after nephrectomy, are atrophic pyelonephritis, hydronephrosis with secondary chronic renal infection, and renal tuberculosis. Of these lesions, unilateral renal atrophy resulting from infection is found most often. Its pathologic characteristics are great reduction in size, widespread fibrosis throughout the renal parenchyma and areal sclerosis involving intrarenal circulation. Atrophy of similar degree may be observed in association with congenital renal hypoplasia, and the histologic distinction between this condition and atrophy resulting from infection may be difficult. Differences in urographic deformity, however, may be of aid in distinguishing these conditions one from the other. Pyelo-ureterectasis and obliteration of one or more calyces usually accompany atrophic pyelonephritis, while diminution in size of the pelvis, calyces and ureter usually is observed with hypoplasia.

The hypertension which occurs in cases of hydronephrosis apparently is related to fibrosis in the renal tissue caused by secondary pyelonephritis. Back pressure from retained urine in the obstructed renal pelvis alone does not affect blood pressure. The possibility that circulatory imba'ance may result from pressure on intrarenal blood vessels, exerted by the dilated renal pelvis and calyces, is not excluded. Since hydronephrosis usually is recognized in the early decades of life, the postoperative results are good unless pyelectasis is bilateral and is so advanced in both kidneys that the renal tissue is cicatricial and is largely destroyed.

The incidence of hypertension in association with renal tuberculosis is less than it is among average individuals and less, moreover, than that observed in association with other so-called surgical lesions of the kidney. Hypertension was found in examination of very few patients with renal tuberculosis observed at the Mayo Clinic. Although only a few such patients were operated on for hypertension, this group is of interest because in most cases the blood pressure returned to normal following nephrectomy and remained normal for the entire postoperative period through which the patients were traced. Among other surgical renal lesions which occurred in association with hypertension were those in a group of cases in which operation previously had been done for lesions such as renal calculus, hydronephrosis, and so on. Postoperative fibrosis and atrophy developed subsequently and involved a large portion of the kidney which had been subjected to operation. Gradually increasing blood pressure was found in each of several cases in which the patients were traced following a recent renal operation. Reduction of blood pressure to normal followed removal of the kidney on which operation previously had been performed. Pyelonephritis of pregnancy is another renal lesion occasionally observed in association with hypertension. Although pyelonephritis of this type usually disappears following labor it may persist in one kidney for years after its onset and may cause renal fibrosis and atrophy.

The postoperative course of hypertension in a series of 60 patients with hypertension who were subjected to nephrectomy from 2 to 5 years after operation was reviewed by Barker and me in 1947[1]. This series has been extended recently to include the postoperative records of 100 hypertensive patients who had been subjected to nephrectomy from 2 to 9 years previously[2]. These patients all had been operated on for relief of hypertension and not because they sought relief from symptoms caused by the renal condition. The postoperative results in these cases were grouped according to the clinical condition; namely, good, fair, poor and death. When the systolic blood pressure, expressed in millimeters of mercury, receded to 150, and the diastolic pressure to less than 100, the result was regarded as *good*. When the systolic pressure was reduced to slightly more than 150, and the diastolic pressure was slightly more than 100, results were regarded as *fair*. *Poor* results included those in which the blood pressure remained at, or slightly less than, the preoperative level. In table 1 it is evident that 64 per cent of the patients traced 2 to 5 years after operation and 53 per cent of the patients traced 5 to 9 years, obtained good or fair results. The importance of following the blood pressure of these patients for a period following nephrectomy is self-

TABLE 1. *Postoperative results: 100 hypertensive patients having severe unilateral renal disease who underwent nephrectomy specifically as treatment for hypertension*

RESULT	TIME AFTER OPERATION	
	2 to 5 years	5 years or more*
Good	45	23
Fair	19	9
Poor	27	16
Death	9	12†
Total	100	60

* Figures in this column based on 60 traced patients.

† Includes the 9 patients who died within two years after nephrectomy.

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[1] Barker, N. W. and Braasch, W. F.: The course of hypertension after nephrectomy for advanced unilateral renal disease. Internat. Abstr. Surg. (Surg. Gynec. & Obst.). **84**: 299–301, 1947.

[2] Barker, N. W.: Hypertension and unilateral renal disease. M. Clin. North America., **35**: 1041–1050, 1951.

evident. Reduction of blood pressure right after nephrectomy does not necessarily indicate recovery from hypertension, since postoperative rest in bed and relaxation may account for temporary reduction. In many cases the blood pressure was greatly reduced immediately following nephrectomy but later gradually returned to its preoperative level. It was thought at first that if the blood pressure remained normal for 1 to 2 years following nephrectomy, the result could be regarded as permanent. However, later clinical records in these cases showed that recurrence of hypertension could be delayed as long as 5 or more years following nephrectomy and might then gradually return to the preoperative level. Reports of reduction of blood pressure following nephrectomy are of little value unless the blood pressure remains normal for at least 2 years.

It is hard to explain why the blood pressure should become normal following nephrectomy, remain so a year or more, and then gradually rise to higher levels. Failure to relieve long-standing hypertension may be attributable to the development of vascular changes from nephrosclerosis in the opposite, or contralateral, kidney. It also is possible that an underlying tendency to hypertension was dormant and that the diseased kidney acted as an immediate stimulant. With removal of the kidney, the immediate stimulus was eliminated and the blood pressure became temporarily normal, but a fundamental essential hypertension subsequently asserted itself. That so-called essential hypertension is an underlying condition in many of these cases is shown by a positive reaction in cold pressor tests in spite of the fact that the blood pressure may have returned to normal after operation.

Clinical and urographic evidence of a unilateral renal lesion in a case of hypertension does not necessarily indicate that nephrectomy is advisable. In fact, insufficient care in selection of patients for operation is the main reason for poor results reported by some surgeons after nephrectomy. Any evidence of disease of the opposite kidney, obtained by clinical examination, roentgenography, urography, or cystoscopy, should be taken as a contraindication to nephrectomy. Uniformly poor results were noted unless the opposite kidney was normal. The advisability of nephrectomy is questionable if examination of the opposite kidney produced any of the following clinical data: 1) Urographic evidence of a former renal lesion as shown by minor dilatation or cicatricial irregularity in the outline of the calyces or pelvis. 2) Absence of compensatory hypertrophy of the renal outline in plain films. 3) The presence of calcific shadows in the renal area. 4) The presence of pus cells in the catheterized urine. 5) Chemical or urographic evidence of abnormal renal function.

Of equal significance is a history of a lesion of, or an operation on, the opposite kidney. In fact, a history of previous disease of either kidney may be equally as important as urographic or any other clinical data. Other clinical factors which serve as contraindications to operation include the following: the patient's age (50 years or more), a cardiac lesion or renal insufficiency, azotemia, a recent cerebral lesion and so on. Removal of the diseased kidney could hardly benefit either hypertension or the patient's general health in the presence of a clinical condition of any of the types just mentioned.

The patient's age is of great importance in the prognosis. Results are best among children and young adults. The chances for reduction in blood pressure among patients who are more than 50 years of age are not good. The duration of the hypertension is also important because, when it is long continued, it affects the arteries of the opposite kidney, causing sclerosis such as is observed in association with chronic nephrosclerosis.

Evidence of failing function of the remaining kidney developed in 9 of the 12 cases in which the patients are reported, in our series, to have died. Increasing values for blood urea were found at intervals of a few months to 2 years following nephrectomy. In several cases the preoperative value for blood urea was at the upper level of normal. In most of these cases there was little or no reduction of blood pressure following nephrectomy.

SUMMARY AND COMMENT

Postoperative results were reviewed in 100 cases in which nephrectomy had been performed for hypertension at least 2 years before; in 60 of these operation had been performed 5 or more years before. The blood pressure returned to normal, or was significantly reduced, in 64 per cent of cases in which the patients were traced from 2 to 5 years, and in 53 per cent of cases in which the patients were traced from 5 to 9 years following operation.

These results should eliminate any doubt as to whether a unilateral renal lesion can cause hypertension and whether removal of the diseased kidney can cause the blood pressure to return to normal.

Careful selection of patients for nephrectomy is essential to good results. Any evidence of a lesion in the other kidney, a patient's advanced age, his unsatisfactory general condition, or the long duration of hypertension can be considered a contraindication to operation.

The three pathologic conditions of the kidney which are most frequently observed in association with hypertension are atrophic pyelonephritis, hydronephrosis with infection and renal tuberculosis. These are the renal lesions, removal of which is followed by the best results.

The blood pressure may drop to normal following nephrectomy, with marked symptomatic benefit, and then gradually return to higher levels with recurrence of symptoms after an interval of from several months to years. In such cases it is possible that nephrosclerosis in the opposite, or supposedly normal, kidney or that a dormant essential hypertension exists, the infected kidney having acted as an immediate stimulant. Removal of the diseased kidney may eliminate this stimulus temporarily but a fundamental hypertension subsequently may assert itself.

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HYPERTENSION DUE TO THROMBOSIS OF THE RENAL ARTERY: REPORT OF A CASE IN WHICH A CURE WAS OBTAINED BY NEPHRECTOMY

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From the Department of Surgery (Urology) College of Medical Evangelists School of Medicine, Los Angeles, Calif.

Hypertension was produced in dogs by Goldblatt in 1934 by reduction of the blood flow through one or both renal arteries. Since the publication of that original work, cures of a similar condition in man by removal of the involved kidney have been reported. This paper presents a case of hypertension caused by reduction in blood flow to the kidney due to thrombosis of the renal artery. The hypertension was relieved by nephrectomy, and the patient's blood pressure has remained normal during the 2 years that have elapsed since operation. The case is of further interest in that a false positive response to dibenamine was obtained, and also because of the unusual and striking retinal changes.

REPORT OF CASE

A 36-year-old Mexican housewife had been apparently well until February 13, 1949, when she was involved in a serious automobile accident which resulted in the death of several persons, including her husband. She was unconscious and was taken to a hospital elsewhere where examination disclosed multiple fractures of the middle third of the right clavicle, of the neck of the first and second ribs, and of the pelvis; also, cerebral contusion. Blood pressure readings during that period of hospitalization were 100, 124, and 132 systolic and 62, 72, and 84 diastolic, respectively. Excretory urograms revealed prompt filling of the left kidney but a nonfunctioning right kidney. She went home after six weeks (about April 20) and gradually regained her strength, although she complained of headache.

On May 6 the patient had a sudden attack of complete loss of vision and severe headache. This condition continued without relief for 2 weeks and she was admitted to the hospital on May 20.

She had had occasional attacks of nausea with vomiting, but denied ever having smoky urine, hematuria, polyuria, dyspnea, edema, chronic cough, or pain in the chest. She had been said to be in good health at the time of a general examination by her family physician in December 1948. She had been married at the age of 15 and had had six children, all of whom were alive and well.

The patient's chief complaint was inability to see. Blood pressure measured on the right side was 220 systolic, 110 diastolic, and on the left 220 and 120; pulse was 100; temperature 98.6F. She had several carious teeth. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion, but an early, high-pitched diastolic murmur was heard at the aortic area and along the left sternal border; the rhythm was regular.

Visual acuity was limited to ability to count fingers at one foot. There was a

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 27, 1951.

watery edema of the conjunctiva. Pupils were round, regular, equal, and reacted to light and accommodation. On examining the fundus, marked edema was noted as well as such marked spasticity of the vessels, that great segments of them were not visible. There were numerous striate and round hemorrhages in both eyes. There were also early star figures as well as cotton wool exudates.

Other physical observations were within normal limits.

The red blood cell count was 3,780,000 with 10.6 gm. hemoglobin; the color index was 0.9. The white blood cell count was 3,700 with 56 per cent neutrophils, 42 per cent lymphocytes, and 2 per cent eosinophils. The sedimentation rate was 49 mm. in one hour. The total serum protein was 6.8 gm. per hundred cc.: albumin 5.1, globulin 1.7. The Wassermann and Kahn reactions were negative for syphilis. The urea clearance test was 64.2 per cent of normal the first hour and 67.5 per cent of normal the second hour. Urinalyses were reported as follows: specific gravity 1.006, 1.020, and 1.007; albumin 3 plus and 4 plus; 2 to 4 red blood cells per high power field; 2 to 4 hyaline casts in one specimen.

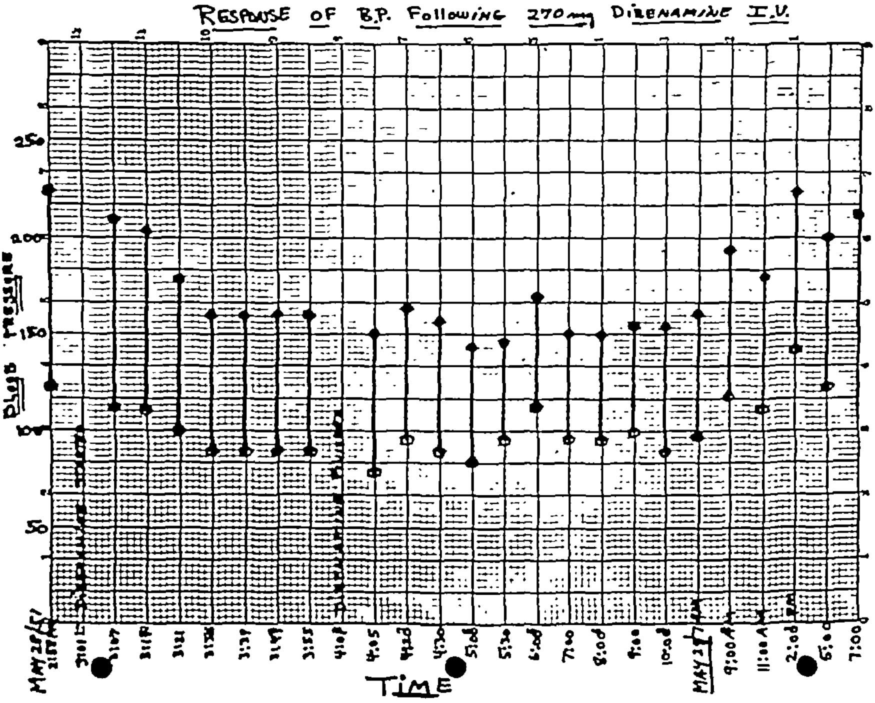

FIG. 1. Graph showing response to dibenamine

A roentgenogram of the skull was normal. That of the chest disclosed residual pleural thickening at the right costophrenic angle and a normal cardiac configuration.

An electrocardiogram indicated a sinus tachycardia and left axis deviation.

Following admittance to the hospital the patient suffered continuous headache and impaired vision. Repeated reading of the blood pressure revealed the systolic to be in the region of 220 and diastolic to range between 110 and 130. On May 28, 270 mg. of dibenamine in 500 cc of a 5 per cent solution of glucose were administered intravenously, and readings of the blood pressure were obtained (fig. 1).

During the first 24 hours following the administration of dibenamine, the blood pressure returned toward normal and the patient's vision improved so that she could distinguish fingers and recognize people about her. Since excretory urography immediately following the injury in February had indicated the right kidney to be a nonfunctioning organ, further urologic studies were carried out. Cystoscopy revealed the bladder to be normal. Indigo carmine injected intravenously appeared from the left ureteral orifice in 4½ minutes in good concentration. Neither urine nor dye appeared from the right ureteral orifice. The right ureter was easily catheterized and obstruction was not encountered. A roentgenogram with the catheter in situ was made and also a right retrograde pyelogram (fig. 2). The left renal contour was outlined fairly well, and the kidney appeared to be larger than normal. The right kidney was small; its surface was fairly smooth. Except for slight blunting of the minor calyces, the architecture of the kidney was normal.

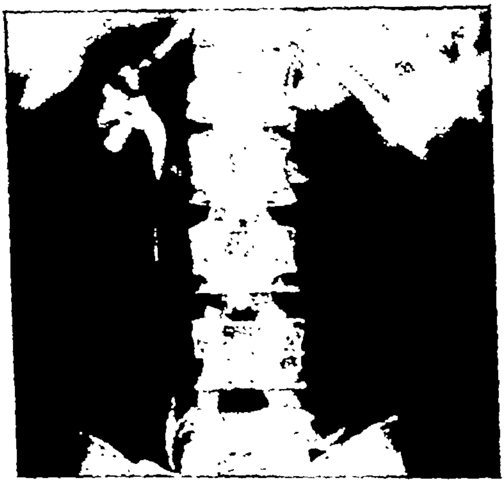

FIG. 2. Retrograde pyelogram

The diagnosis suggested was atrophic kidney secondary to a thrombosis of the renal artery, probably on a traumatic basis. In the differential diagnosis a congenital hypoplastic kidney had to be considered, and because of the positive response to dibenamine it was believed that a pheochromocytoma could not be excluded.

On June 8, through an extraperitoneal lumbar incision and resection of the twelfth rib, a right nephrectomy and exploration of the right adrenal was carried out. The kidney was shrunken to approximately one-third the average size and was firm in consistency (fig. 3). The absence of pitting and of contraction of scar tissue pointed to the disease process as of fairly recent origin. The most striking observation was the renal artery: This did not pulsate and it was represented as

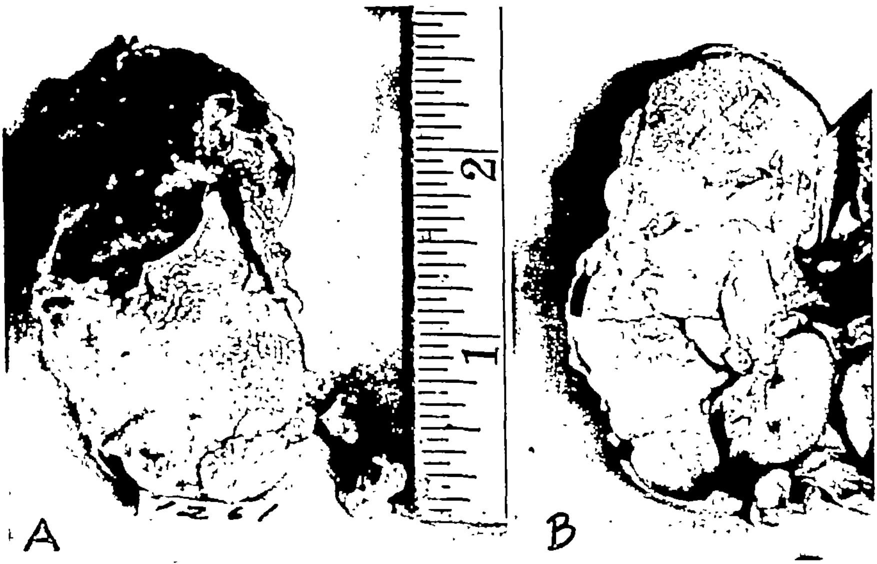

FIG. 3. Specimen removed at operation

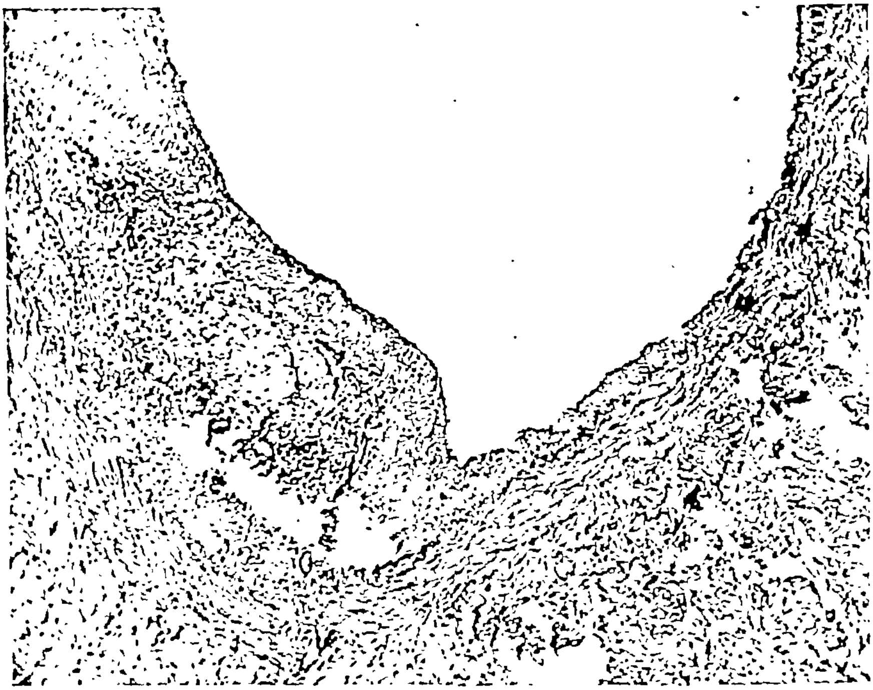

FIG. 4. Section of renal artery showing mural thrombus

a fibrous cord. The right adrenal gland was atrophied; an adrenal tumor was not found.

At the conclusion of this procedure the patient was turned over, and the left adrenal gland was explored through a smaller similar incision. The left adrenal appeared to be slightly enlarged, probably a result of compensatory hypertrophy. It was firm in consistency, but palpation as well as biopsy did not disclose tumor formation.

Pathological report: The right kidney was approximately 6.5 cm. long, 3 cm. wide, and 2.5 cm. thick. There was no pitting on the surface of the kidney and no gross area of infarction. The ureter and the renal vein seemed normal. At the hilum the renal artery appeared to be divided into several small branches which entered the kidney in the usual position around the renal vein. In sections taken through the numerous small arteries at the renal pelvis, definite thickening of the arterial walls was noted. Section of the renal artery showed a mural thrombus (fig. 4). In sections taken through the renal cortex (fig. 5) a marked interstitial fibrosis involving both the cortical and the tubular areas was seen. In the cortical areas the fibrosis and the fibrous replacement of many of the glomeruli seemed to be in isolated areas. However, the interstitial fibrosis was generalized and fairly

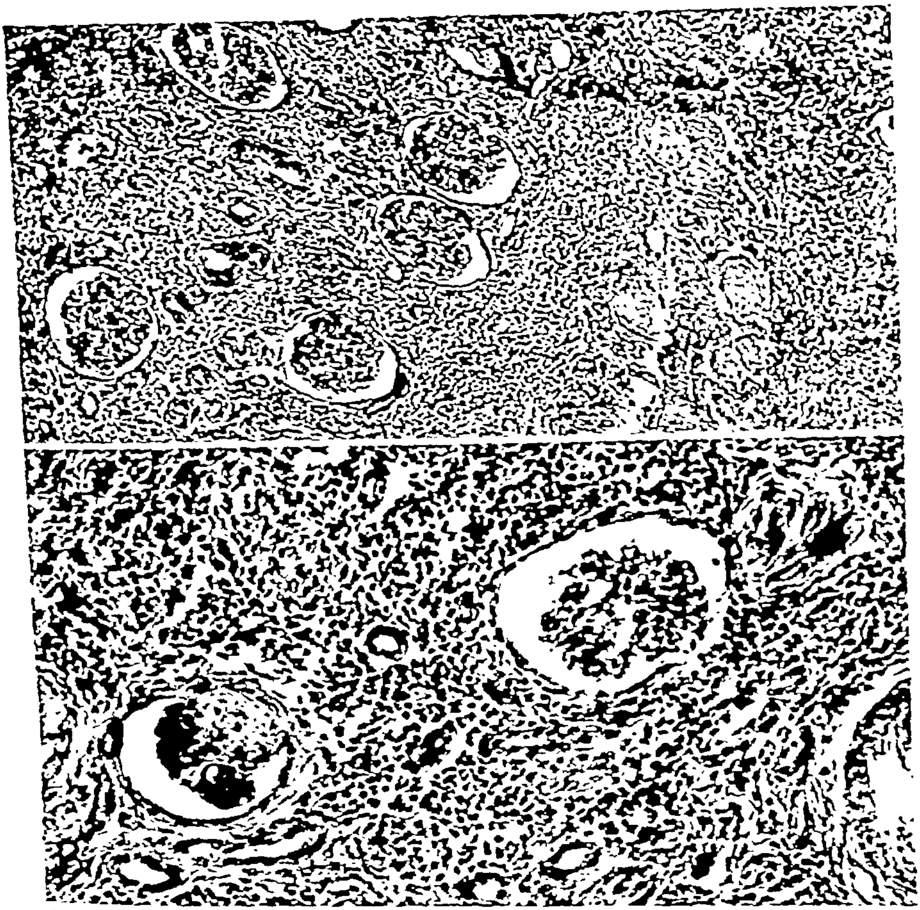

FIG. 5. *A*, (top) showing zone of intact and hyalinized glomeruli. Low power. *B*, (bottom) showing progressive stages in hyalinization of glomeruli. High power.

well distributed throughout the entire kidney. There were many casts in the tubular area. The pathologic diagnosis was chronic atrophic pyelonephritis due to thrombosis of the renal artery.

The postoperative course was entirely uneventful, both wounds healing by primary union. The blood pressure dropped to normal immediately following the nephrectomy and remained within normal limits. The patient's vision began to improve at once and continued to improve while in the hospital. She was discharged on the tenth postoperative day at which time her blood pressure was 110 systolic, 70 diastolic.

Since discharge, the patient has been seen on numerous occasions, and her vision has improved so that she can do all her own housework and read the newspaper. The edema of the retina has completely disappeared, but several small areas of scarring persist. Six months after surgery there was some narrowing of the vessels and irregularity in their caliber. Her vision was 20/80 in both eyes with correction. Her blood pressure has remained at 110 to 120 systolic and 70 to 80 diastolic during the 2 years' elapse since operation.

SUMMARY

A case of hypertension due to thrombosis of the right renal artery in which a cure was obtained by nephrectomy is reported. The hypertension in this instance simulates the conditions instituted in animals by the use of the Goldblatt clamp. The clinical history points to trauma as the likely cause of the thrombosis. The striking retinal changes and the false positive response to dibenamine in this case are of unusual interest.

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RENAL BISECTION

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Extensive nephrotomy incisions as avenues of attack on large branching renal calculi are now seldom employed. This surgical technique fell into disfavor and disuse as a result of a relatively high incidence of complications. Most important among these were hemorrhage, both primary and delayed, which necessitated early secondary nephrectomy as a life-saving procedure in a high percentage of cases; renal cortical sepsis, characterized by an exceedingly stormy postoperative course and further destruction of functioning tissue; and lastly, the destruction of renal parenchyma by incision, and more particularly by the hemostatic sutures thought necessary to control bleeding.

In consequence, a conservative or nonsurgical method of management was adopted for certain cases. Where symptoms were produced by the presence of a large dendritic calculus in one kidney, with no apparent involvement of the other, nephrectomy was considered justifiable. The rapidity with which stones may form in the remaining kidney, apparently normal at the time its mate was removed, attests to the shortsightedness of this policy, which ignores the basically metabolic character of stone disease. Projecting this conservative attitude further, where the condition was bilateral, or if such stone formation occurred in a solitary kidney, it was thought that only expectant or the so-called "medical" therapy would in the long run insure the greatest good to the greatest number of victims so afflicted at the least cost in life and morbidity. How effective such therapy actually was is shown in the series of bilateral staghorn disease cited by Priestley which were not operated upon and of which but few were alive 10 years after the diagnosis had been made.

Yet, while such a program seemed to compromise the urologist's primary obligation to conserve renal tissue, in effect, because of the operative risks involved to the remaining renal substance, it accomplished its purpose, if only by indirection. Such negative therapy could do nothing to arrest the unremitting processes of kidney destruction which ultimately resulted in progressive renal insufficiency and death in renal failure. The newer methods of control of recurrence devised by Shorr justify a re-examination of the problem of removal of large calculi.

Various techniques for nephrotomy for large dendritic stones have been described. Of these, three are noteworthy. All aimed at maximum exposure of the stone at least cost in renal substance and hemorrhage. Cullen and Derge in 1909 described a technique in which they employed a pliable silver wire of low tensile strength as a saw for the purpose of halving the kidney from within outward. They maintained that when the wire was used to open the kidney in such a manner, the wire had the effect of pushing aside rather than cutting

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across the arborizing blood vessels, especially the arteries, which have firm coats of considerable resistance. The wire was introduced into the kidney through a small incision in the renal pelvis on two blunt-ended curved or straight needles, each of which was pushed through the parenchyma via the superior and inferior calyces respectively. The fibrous capsule between the points of emergence of the two needles was cut with a scalpel, and the wire then drawn gently back and forth in the operator's hands until the kidney was halved. I have not used this method, and it is not widely used even by those urologists who perform nephrotomy for stone. It would appear, however, that the tearing action of the silver wire saw results in greater damage to the kidney than does a well-directed sharp incision with the scalpel. Further, the technical difficulties in placing the wire through the pelvis and calyces containing a ramifying calculus limit the value of the procedure. Figure 1, from *Diseases of the Kidneys, Ureters and Bladder*, by Kelly and Burnam, demonstrates this method of nephrotomy.

A second, more commonly used technique of nephrotomy is that described by Prather in 1934, and is known as the V type of nephrotomy. In this technique, the renal pedicle is clamped for hemostasis, and a V incision is made on the posterior aspect of the kidney, the apex of the V commencing at the sinus renalis. Although this incision results in adequate exposure of the pelvis and calyces, I have hesitated to use it because I believe that there is a very real danger of causing injury to the retropelvic vessels with a consequent reduction in renal reserve as a result of the ischemia and late scarring in the area supplied by these vessels. Support is given to this belief by Deming who demonstrated in corrosion models that ligation of the retropelvic vessels causes renal damage which is not reparable in four months. Belt and Joelson in 1925 were also able to show that ligation of the retropelvic artery caused avascularization and scarring that was irreversible.

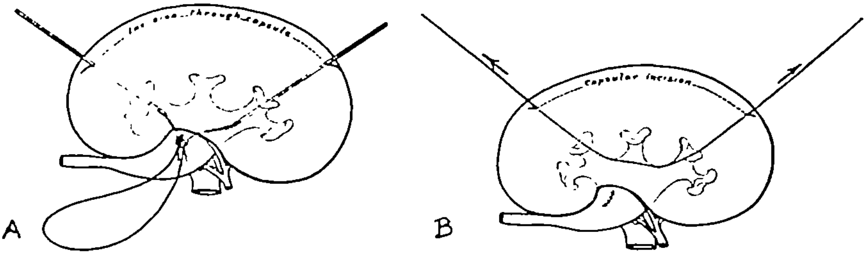

FIG. 1. *A*, silver wire method of nephrotomy. Silver wire is introduced into kidney through small opening in renal pelvis on two blunt-ended needles, each of which is pushed through parenchyma through superior and inferior calyces respectively. Fibrous capsule between points of emergence of two needles is cut with scalpel. *B*, silver wire method of nephrotomy. Opening in pelvis is closed, and wire drawn back and forth in operator's hands until split is completed.

Lowsley's method of nephrotomy, involving the use of capsular sutures of wide ribbon-gut for the purpose of re-approximation of the kidney, has been successfully employed. No parenchymal mattresses are used, however, and hemostasis is dependent upon the use of tabs of fat. Microscopic sections of wounds closed by this method show that the glomeruli are normal adjacent to the scar, and that practically no compression necrosis results when this technique is properly employed. From the description of the technique by the author, it appears that the method is most suitable when the nephrotomy is only of limited extent, so that the closure is effected with but one ribbon-gut suture. I feel that polar incisions, as advocated by this author, could not be used in the case of large calculi or multiple small calculi in minor calyces. It would appear that larger nephrotomy incisions might be repaired with several such sutures, but I have not felt the attempt warranted because of the success I have had with the method presently to be described, and further because of the theoretical possibility of hemorrhage from a failure to use parenchymal hemostatic sutures. I am indebted to Lowsley however for the idea of using ribbon-gut in closure of nephrotomy incisions.

Extensive nephrotomy incisions for stone with the modifications to be described were first employed by the author in those cases in which there existed no other alternative but the proximate death of the patient as a result of calculus disease. Initial results were sufficiently encouraging to warrant extending the indications to include cases of less desperate urgency in the hope of salvaging even more functioning tissue. It is now my conviction, based on the results in these cases, that surgery is indicated in every case where a diagnosis of calculus disease is made; that the presence of a stone in the kidney too large to pass spontaneously, however "silent" it may be as regards symptoms, constitutes the primary indication for surgery. Certainly, the recuperative powers of a stone-bearing, uninfected, relatively normally functioning kidney as regards surgery are undeniably better than when the calculus-containing kidney begins to approximate a pyonephrotic sac. Kidney substance destroyed by stone is irretrievably lost, and the optimum time to effect renal salvage is the earliest time at which the diagnosis of renal calculus disease is made.

The series under consideration consists of 80 cases. In these cases, extensive nephrotomy involving two thirds and more of the convex border of the kidney, was performed in 16 cases in which large stag-horn stones were present bilaterally, and in 8 cases in which the condition was present in a solitary kidney, its counterpart in each case having been previously removed because of advanced stone disease. There has been but one instance of delayed hemorrhage, and this responded to supportive therapy. The late bleeding in this case was thought attributable to the experimental omission of the capsular suture which will be described later. There has been but one death, this occurring in a 56 year old white man within 24 hours of operation on a solitary kidney. Following operation, and prior to his death, he had drained 800 cc of blood-tinged urine from his nephrostomy tube. Diagnosis was massive atelectasis of the lung.

The generally satisfactory results that have been obtained with nephrotomy in these cases, in contrast with those reported in earlier series, are believed to be due to four factors. First is the development of a technique that minimizes both blood loss and the strangulation of functioning renal substance. Second, the role of chemotherapy and antibiotics in eventuating a favorable outcome cannot be overemphasized. Third, the ready availability of blood for the purpose of replacement and in prophylaxis against operative shock and its attendant renal suppression is a relatively recent blessing. Fourth, the newer knowledge of renal physiology and its application in maintaining water and electrolyte balance by intravenous infusion is an advantage that was denied to earlier surgeons.

The technique of nephrotomy for large dendritic calculus as performed by the author is as follows: After the classical kidney incision has been made and the renal fascial envelope opened, the kidney itself is carefully mobilized, the greatest caution being exercised to prevent its decapsulation. After the pedicle has been thinned down sufficiently, a curved, rubber-shod 9 inch Doyen intestinal clamp is placed to encompass the pedicle, is closed, and is left undisturbed until just before the cut margins of the kidney are to be re-approximated. No harmful effects have been noted as a result of this continued compression, and this belief is supported by the work of Litten on the effects of temporary anemia on the kidney. He found the extreme limit of tolerance to anemia to be 1½ hours before any serious and irreversible changes occurred in the kidney. I have left the pedicle clamp undisturbed for one hour and eighteen minutes in one case with no obvious untoward effect on subsequent function as measured by excretion urography. The investigations of Papin and Ambard, Eisendrath and Strauss, Hubner, and Marshall and Crane also testify to the safety of such prolonged compression.

Following compression of the pedicle as described, sagittal incision is made into the cortex, in the so-called avascular line of Brödel, its extent depending upon the size and ramifications of the stone to be removed. Incision is made into this line on theoretical grounds, since the arborizing blood vessels are alleged to be least in number in this area. While corrosion models actually demonstrate the existence of such a line, in practice it is extremely difficult to locate, and in only four instances have I felt that I had made the incision in a bloodless area.

The incision is carried down to the stone, and the kidney laid open. Every effort is directed at removing the stone intact whenever possible, and the binding calicular necks are incised with the scalpel to permit the mobilization of as many dendrites as possible with the main body of the stone. After the stone is finally removed, careful exploration of every calyx is carried out with the finger, probe, and spoon, and all remaining bits of calculus are removed. The advantages that accrue to the use of x-rays taken at the operating table for the purpose of checking the completeness of extraction are obvious. The calyces are then irrigated and aspirated, and preparation made for closure (fig. 2).

Inspection of the opened kidney at this point will reveal the presence of variable numbers and sizes of blood vessels that have been divided. No effort is made to clamp these; instead, each is secured with a suture-ligature of five zero atraumatic intestinal catgut. Two to four such ligatures will be placed at this time. This done, the Doyen clamp is opened for a moment. An immediate oozing of dark venous blood occurs, but this causes no concern, since it is usually not copious in amount. But here and there, through this darker blood, streaks of bright arterial blood can be seen. As each streak is successively traced to its point of origin, the pedicle clamp is closed and the bleeding point secured by fine suture-ligature. Again, three or four such suture ligatures may be necessary. Finally, only the venous oozing is seen as the pedicle clamp is released. After observing the kidney for a few moments, the clamp is closed again and the kidney closure begun.

I believe that the foregoing attempts at producing hemostasis are closely related to the absence of immediate postoperative hemorrhage in this series. As a further benefit, such hemostasis permits the more superficial placement of the hemostatic mattress sutures to be described and thus reduces the incidence of delayed hemorrhage resulting from the strangulation of larger amounts of kidney tissue when the mattress sutures are more deeply placed.

The first step in the re-approximation of the cut halves of the kidney is the placement of a running lock-stitch for the closure of the capsule. This suture begins at either pole of the incision and proceeds to the center where it is tied. A 24F four-wing Malecot catheter is then placed in the renal pelvis, and the capsular suture completed. Five zero atraumatic chromic catgut is used, and the inclusion of parenchyma in the suture is avoided. I believe that placement of the capsular suture as a preliminary to the use of the deeper mattress sutures is desirable because of the simplicity with which both halves of the kidney can be re-aligned, and more important, because with the deeper sutures placed first, it becomes almost impossible to reapproximate the capsule (fig. 3).

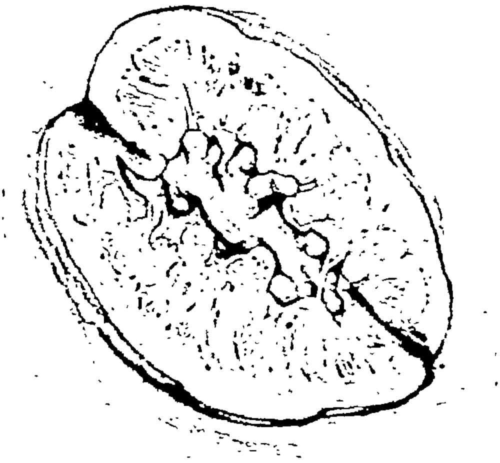

FIG. 2

The capsular suture completed, five zero atraumatic chromic catgut sutures on straight intestinal needles are then placed as vertical mattresses no more than one to one and one half centimeters below the incision. The loop of the mattress engages on one side of the kidney a 1 cm. wide long strip of ribbon-gut that runs from pole to pole, and the suture is tied over a similar strip that has been placed on the other side of the kidney (fig. 4).

Great care is taken to tie these hemostatic sutures loosely, since with the compressing pedicle clamp removed, the kidney will increase as much as 25 per cent in size, causing tighter sutures to strangulate the intervening tissue. Generally six to eight such sutures are necessary to effect complete hémostasis. When these have been placed and the clamp opened, the incisional site remains dry. In the event of bleeding at any point, an additional mattress suture is placed. In my experience, such additional hemostatic sutures have seldom been necessary. When fully satisfied that bleeding has been controlled, the pedicle clamp is removed, the kidney replaced, Penrose drains inserted, and the wound closed in the usual fashion. During the course of the wound closure, it is a common experience to see bloody urine draining from the nephrostomy tube.

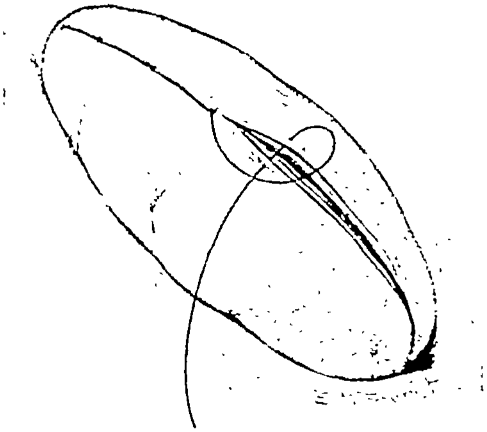

Fig. 3

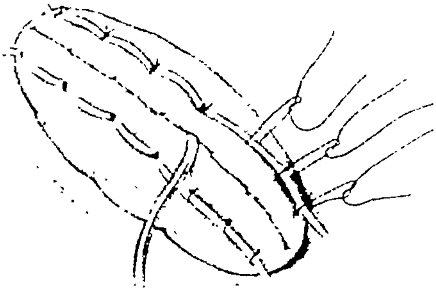

Fig. 4

I prefer the use of ribbon-gut to that of tabs of fat or muscle to reinforce the mattress sutures for at least two reasons: first, the hemostatic suture cannot tear through it; second, and more important, the continuous strip has the effect of converting the individual sutures into a solid unit of compression, with each suture supported by its mates all along the line.

The limitation of space denies the opportunity to present illustrative cases with any great amount of detail. Suffice it to say that with the exception of the one fatality, all of the patients in this series are alive and had normal nitrogen chemistries at time of discharge. The following cases are presented as some of the more extreme problems in this series.

CASE REPORTS

Case 1 (*fig. 5*). C. D., B. H. No. 10142–47, a 59 year old white man, was admitted to the Bellevue urological service in uremia and complaining of pain in both costovertebral angles and flank tenderness. He admitted to the knowledge that he had had bilateral kidney stones for 10 years, at which time a right nephrolithotomy and ureterolithotomy had been performed. Five years prior to admission, another right ureterolithotomy had been done. Since the last operation, he had had frequent attacks of bilateral flank pain associated with nausea and vomiting, and for 5 days prior to admission, he had constant bilateral flank pain associated with nausea, vomiting, hematuria and dysuria. On admission, his nonprotein nitrogen was 180 mg. per 100 cc. He was found to have 600 cc of residual urine. Twenty days after admission, left nephrolithotomy and suprapubic cystotomy were done. After an interval of 2 months, the right kidney was similarly operated upon. It is of interest to note that in addition to the removal of the large calculus, a cystic area of the lower pole of this kidney, which on section was found to contain a blackish grumous material, was resected and subsequently reported as a papillary cystadenoma of the kidney. Chemical analysis of calculi revealed calcium phosphate and calcium carbonate. The patient withstood surgery well on both occasions, and 5 months after initial admission, a transurethral resection of the prostate was performed. On discharge from the hospital, he was voiding well, had nonprotein nitrogen of 30 mg. per 100 cc and was carrying a 30 cc residual. He was sent to the Shorr Clinic but refused to take amphojel and persisted in the ingestion of 2 quarts of milk daily. His last clinic visit was June 27, 1950 at which time recurrence was present.

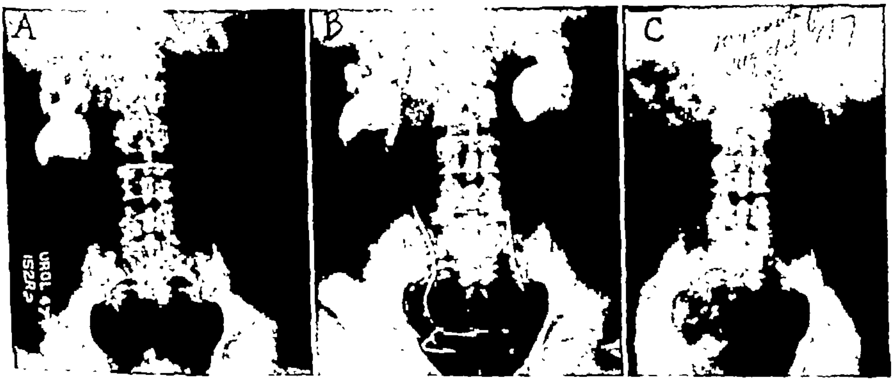

FIG. 5. Case 1. *A*, plain urogram following bisection of left kidney. *B*, plain urogram with catheter in place. *C*, postoperative bilateral renal bisection. Twenty minute excretory urogram shows function bilaterally.

Case 2 (*fig. 6*). J. G., L. H. H. No. 123245, a 28 year old white man, presented himself with the complaints of left renal colic and hematuria. His history indicated that he had been having intermittent attacks of renal colic for 19 years. A right nephrectomy had been done in 1935 because the kidney was filled with 20 stones, according to the patient. Two months later, a left nephrotomy was performed for the removal of calculi. Since that time, he had had intermittent attacks of left renal colic and hematuria. On January 8, 1948, a left nephrotomy was done and one large calculus and 80 smaller faceted stones were removed. Preoperatively, the blood urea nitrogen was 20 mg. per 100 cc and 17 days postoperatively was 17 mg. per 100 cc. Analysis of the stone showed is to be composed largely of calcium oxalate. The patient remained in the hospital a total of 23 days, and returned to his job 6 weeks postoperatively. An excretory urogram taken January 18, 1951 showed excellent function and no evidence of recurrence.

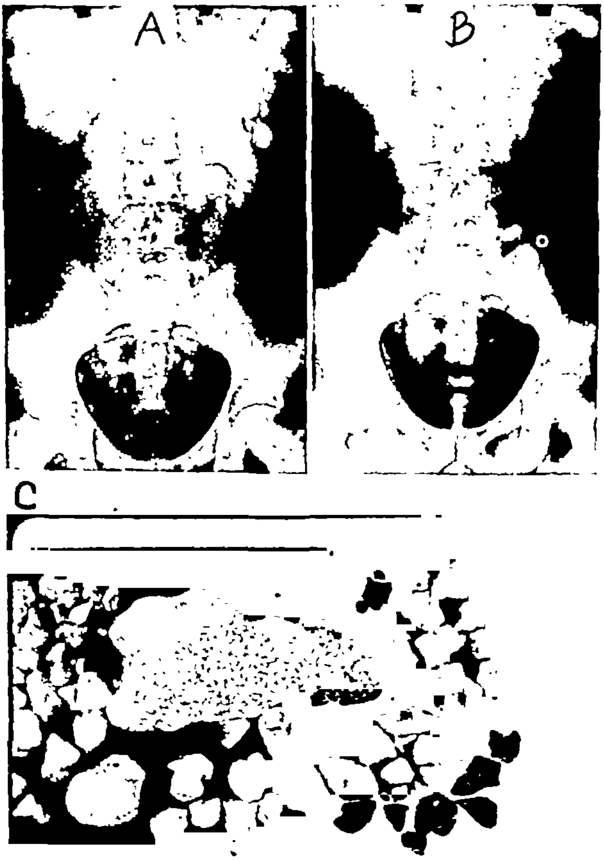

FIG. 6. Case 2. *A*, plain urogram shows solitary left kidney. *B*, postoperative plain urogram. *C*, large calculus and faceted smaller calculi.

Case 3 (*fig. 7*). J. B., L. H. H. No. 32032-50, a 45 year old white man, presented himself in anuria. This had been constant for 96 hours except during a 14 hour period of flying between Shannon, Ireland, Gander and New York. On arrival he again became completely anuric. Past history revealed a knowledge of bilateral calculi since 1942. He had undergone a left nephrectomy in January 1947, for calculi. Examination revealed one large and one small right renal calculus and a lower right ureteral calculus. Blood urea nitrogen 57.9 mg. per 100 cc. A 6F catheter was passed to the kidney and left indwelling. The catheter was expelled spontaneously 3 days later. Voiding was adequate for 3 days when anuria recurred. On cystoscopy April 7, 1950, a ureteral catheter could not be passed, but the stone was dislodged and urine could be seen coming from the orifice. Anuria did not again recur. On April 10 the blood urea nitrogen was 19.1 mg. per 100 cc. He was discharged April 15 to attend to business obligations. He was re-admitted May 8. He was voiding well. The blood urea nitrogen was 19.4 mg. per 100 cc. May 10, a renal bisection was performed by the method described; operating time 1 hour, 51 minutes. The initial blood pressure was

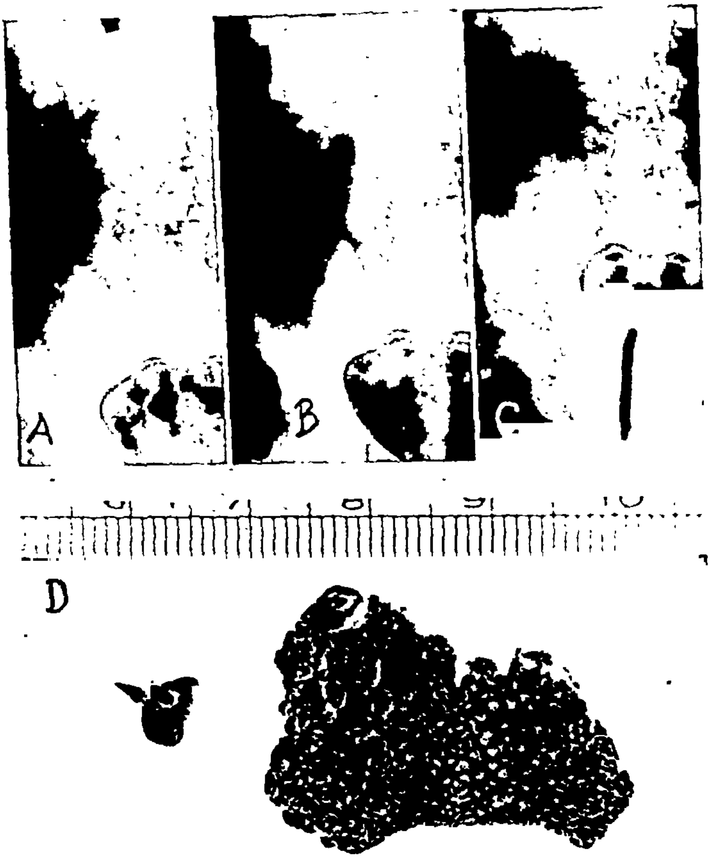

Fig. 7. Case 3. *A*, plain urogram, *B*, thirty minute excretory urogram shows change in position of large calculus, also low ureteral calculus. *C*, right ureterogram shows kidney and ureter now free of calculi. *D*, shows unusual formation of calculi.

120/76; at the conclusion of the procedure, 110/70. Analysis of calculi showed calcium oxylate. Note by resident (May 11): "Urine is clear. General condition excellent." May 23, cystoscopy and right retrograde pyelogram were done. The ureteral calculus no longer was present. The nephrostomy tube was removed May 24, and the patient discharged 2 days later. June 2, blood urea nitrogen 14.8 mg. per 100 cc. The patient returned to Europe June 30, 1950. At last communication (April 19, 1951) he had no complaints. Incidentally, symptoms of duodenal ulcer treated for 3 years prior to operation have completely disappeared.

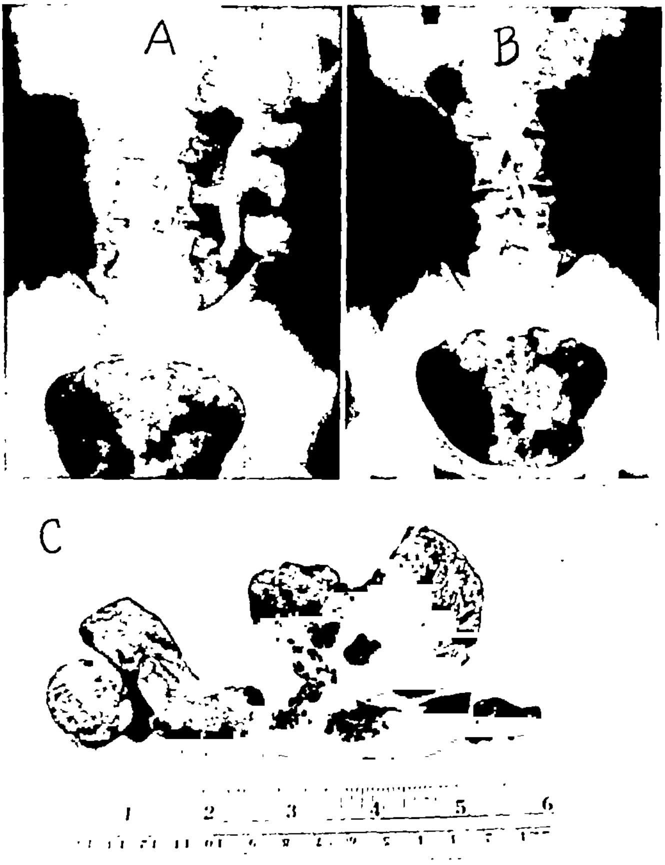

FIG. 8. Case 4. *A*, plain urogram shows large left renal calculus with small oval calculus in upper calyx, also 1 cm. right renal calculus. *B*, postoperative plain urogram. *C*, large left renal calculus and smaller calculus from upper calyx.

Case 4 (*fig. 8*). J. B., L. H. H. No. 145739–50, a 56 year old white man, was admitted August 21, 1950 after 1 week of severe left flank pain. His first symptoms (left renal colic and hematuria) were noted in November 1949. A diagnosis of bilateral calculus disease made but operation was refused. Since that time the patient has suffered from chronic mild left flank pain with radiation to the left groin. Cystoscopy and pyelograms on August 21 revealed a very large left renal calculus and a small oval calculus in the upper calyx of the kidney, and a 1 cm. calculus in the lower calyx of the right kidney. No indigo carmine appeared in 10 minutes from the left side; deep concentration on the right in 3 minutes. August 21, 1950, blood urea nitrogen 9.7 mg. per 100 cc, calcium 10.4 mg. per 100 cc, phosphorus inorganic 3.0 mg. per 100 cc. Operation was performed August 25 by the described method. Upon opening the upper calyx a discharge of purulent urine was obtained under pressure. The initial blood pressure was 110/80; at the conclusion of the procedure, 100/80. Analysis of calculus showed calcium phosphate. The nephrostomy tube drained 500 to 900 cc of urine in 24 hours and on September 6 the tube was removed. Blood urea nitrogen 14.6 mg. per 100 cc. The patient was discharged September 10 to the clinic and put on Shorr regimen. An excretory urogram December 11 showed fair function on the left side, and excellent concentration on the right side.

SUMMARY

A positive surgical approach to the management of large branched renal calculi, employing a technique such as has been described is warranted early and in the interest of preserving renal function. This holds true also in the presence of bilateral staghorn stone disease, as well as in the case in which the condition exists in a solitary kidney. The progressive renal damage that occurs, regardless of whether or not symptoms are produced, justifies surgical intervention when the diagnosis is made. The low operative risk coupled with the justifiable expectation of favorable results in the large majority of cases warrants the suggestion that a general re-appraisal of the technique of nephrotomy in the management of such cases as have been described is in order. With the accumulation of statistics indicating the effectiveness of medical therapy in the prevention of recurrence as described by Shorr and others, additional stimulus is provided for the conservation of renal tissue through early surgery.

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USE AND ABUSE OF PARENTERAL THERAPY

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In order that the body cells will function with maximum efficiency they require a plentiful supply of food, the prompt removal of the waste products of their metabolic activities, and their water and electrolyte contents must be maintained within certain narrow limits. To ensure that adequate amounts of food, electrolytes and water are readily available to the cells, they are surrounded by a large volume of interstitial fluid. This fluid is equilibrated with the blood plasma which connects it with the various excretory organs of the body so that the volume and composition of the interstitial fluid can be regulated. Thus the body fluid is divided between two large compartments, the intracellular and the extracellular; the latter compartment being further separated into the interstitial and the intravascular sections. In the adult the intracellular fluid measures approximately 30 to 35 litres and the total extracellular fluid 18 to 20 litres of which 3.5 litres are circulating as plasma in the intravascular section. The fluid in the interstitial space should be concerned primarily with regulating the volume and composition of the intracellular fluid. Unfortunately, for mechanical reasons, it is more important to maintain a normal volume of blood plasma than of interstitial fluid and so, if the excretory mechanisms of the body cannot compensate for abnormalities in the volume of circulating plasma, such changes in volume are corrected from the interstitial fluid. This will eventually lead to alterations in the intracellular fluid and so the functioning ability of the cells will be affected.

Of the four organs of excretion, namely the kidneys, lungs, skin and gastrointestinal tract, the kidneys are the most important. Depending upon requirements of the body and within certain limitations, they are able to select the fluid and electrolytes they will discard. This ability of the kidneys to compensate for excesses of both fluid and electrolytes explains why the majority of patients are able to tolerate the large volumes of electrolyte solutions which, in every branch of medicine, it appears to be the fashion to administer parenterally.

In the practice of urology, we are concerned mainly with the treatment of diseases of the genito-urinary tract, and in many instances this all important regulating mechanism has become functionally inefficient. Therefore, when required to restore a disturbed fluid and electrolyte balance, the urologist must accurately compute both the amount of fluid and the type of electrolytes which are to be administered parenterally. Failure to do this will place extra strain on poorly functioning kidneys and require them to exert selections which are beyond their capabilities. The amount of fluid required will depend on the present state of hydration of the patient. When this has been restored to normal limits it will only be necessary to administer sufficient fluids to replace the anticipated losses (table 1). The average daily waste products of the metabolism of an adult can

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be eliminated in 350 ml. of insensible perspiration from the lungs and skin, and 600 ml. of urine from adequate functioning kidneys. Thus the normal adult requires a minimum of approximately 1 litre of fluid every 24 hours to enable him to excrete the metabolites normally produced during this period. This litre does not allow for any further losses in the urine, feces or sweat which can easily amount to an additional litre per day. Therefore if a normal adult has to be denied the ingestion of food and fluid, we suggest as a working rule that he receive parenterally at least 2 litres of fluid daily. In addition, whatever is lost by diarrhea, vomiting, continuous gastric suction, excessive sweating or discharging sinuses, etc. should be supplied millilitre for millilitre. Most of these extra losses can be measured, but it is difficult to evaluate sensible perspiration and it is not generally appreciated that patients can lose large volumes of water per day by sweating, especially when confined for long periods in humid atmospheres such as one finds in operating rooms.

TABLE 1. *Fluids lost from the body in 24 hours. After Adolf, E. F.: Physiol. Rev., 13: 356, 1933.*

Urine	600 to 2000 ml.
Insensible perspiration	350 to 700 ml.
Minimum vital loss	950 ml.
Sensible perspiration	50 to 4000 ml.
Feces	50 to 200 ml.
Total daily loss approx	1 litre to 7 litres

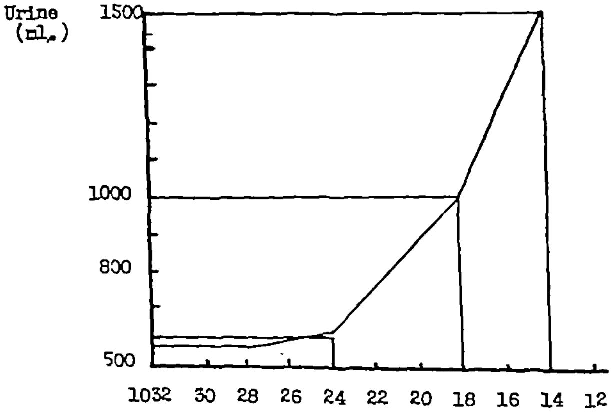

FIG. 1. Relation between urine volume and maximum attainable specific gravity to excrete 35 gm. waste. Lowermost line of figures represents specific gravity. After Marriott, H. L.: Am. Lect. Series, No. 32. Springfield, Ill., C. C. Thomas.

The accurate replacement of fluid is especially important when a kidney lesion is the cause of anuria. If the anuric patient has no measurable fluid loss his intake should never exceed 1 litre per day. Additional losses through vomiting or diarrhea etc. should be replaced quantitatively.

In diseases where the concentrating power of the kidneys is impaired the patient will not be able to eliminate the metabolites in 600 ml. of urine and will require increasing amounts of fluid as the maximum attainable specific gravity of the urine decreases (fig. 1). Diminished renal concentrating power is common in obstruction due to prostatic hypertrophy so such a patient requires a larger daily fluid intake than the normal healthy individual. In addition it must be remembered that protein catabolism is increased in disease and so more water products are presented to the kidney for elimination, thus the patient must excrete even more urine to maintain his nonprotein nitrogen within normal limits.

Clinical dehydration will follow either the failure to ingest water in adequate amounts or its loss in excessive quantities. The most frequent cause of dehydration is failure to ingest adequate amounts of fluid. This is especially common with the seriously debilitated patient who is unable to help himself to water, even though it is supplied on his bedside table. These patients require much more individual attention than is often possible and in such cases it is advisable to prescribe a minimum of 3 ounces of fluid every hour as a medicine, for the nurse or relative will consider it important to administer a medicine on time but may not be as conscientious about an order to give frequent drinks.

Dehydration from excessive loss of water rarely occurs in clinical practice, as fluids lost from the body usually contain dissolved electrolytes and have the same osmotic pressure as the body fluids. The term "dehydration" is used to describe the clinical state which follows both deficiency of water alone and deficiency of water and salts in isotonic strength, but it is important to distinguish between these two states as the effect on the osmotic pressure of the body fluids differs in each condition.

TABLE 2. *Body fluid compartments*

Extracellular (17.5 litres)				*Intracellular (30 to 35 litres)*
Plasma (3.5 litres)	*Cap. Wall*	*Interstitial 14 litres*	*Cell. Membr.*	*Intracellular*
Protein				Protein
Sodium	⇌	Sodium		Potassium
Chloride	⇌	Chloride		Phosphate
Bicarb.	⇌	Bicarb.		Cl. & HCO_3
Water	⇌	Water	⇌	Water

The fluids in the various compartments of the body are in osmotic equilibrium but the electrolyte content of these fluids differs. The capillary wall is readily permeable to all electrolytes of the plasma but protein, whilst the cell wall is only readily permeable to water (table 2). The effects of either pure water or pure salt loss can be simply demonstrated from this scheme.

If the water is not supplied in adequate amounts or if only water is lost from the plasma, the tonicity of this fluid will increase and water will pass from the interstitial fluid into the plasma to restore isotonicity and plasma volume. The interstititial fluid will then become more hypertonic than the intracellular fluid and water will pass from the cell, so producing "intracellular dehydration." The chief symptom of "intracellular dehydration" is thirst and as this is the normal protection against dehydration it should never be disregarded. Thirst must be interpreted as an increased demand for water. If hypertonic solutions such as 5 per cent glucose in saline are administered to such a patient the tonicity of the plasma will be increased and the condition worsened rather than improved. As chief regulating mechanism of the body, the kidney attempts to restore isotonicity but to accomplish this it must excrete electrolytes and conserve water. This is an impossible situation, for the kidney cannot act like a salt shaker and excrete solid sodium chloride and so, in attempting to restore the balance, it excretes more water and so further depletes the plasma volume thereby completing a vicious cycle (fig. 2). When renal concentrating power is impaired more fluid must be eliminated to excrete the same amount of salts and so this vicious cycle is further accelerated. Hemoconcentration itself decreases glomerular filtration rate and leads to inadequate elimination of metabolites. If the ensuing uremia is accompanied by vomiting, dehydration will be further increased and the cycle shown in figure 3 will ensue.

Both fluid and electrolytes are lost in vomiting, continuous gastric suction, etc. and there is an increased excretion of base from the plasma when the kidney is damaged and is unable to synthesize ammonia. Thus the chemical composition of the fluid lost is important, for there will be a tendency towards alterations in the pH of the body fluid depending on whether more basic acid radicals are lost. The body fluids are almost neutral in reaction and therefore all the basic radicals, or cations, must be combined with the acid radicals or anions to form neutral salts. Blood plasma is the only part of the body fluids which can be sampled easily, and because all the body fluids are in equilibrium a fairly satisfactory picture of the electrolytes of the body can be obtained by balancing the anions and cations of the plasma. In order to do this it is necessary to express each electrolyte of the plasma in equivalent units. As one equivalent weight (E.W.) $\left(\frac{\text{Mol. Wt.}}{\text{Valency}}\right)$ of an alkali exactly neutralizes one E.W. of an acid the various ions in a volume of plasma must be expressed in equivalent weights. The unit used is the milli-equivalent per litre.

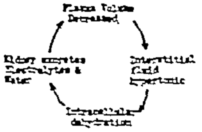
Plasma Volume Decreased
Interstitial Fluid Hypertonic
Intracellular dehydration
Kidney excretes Electrolytes & Water

FIG. 2. Pure water loss. After Marriott.

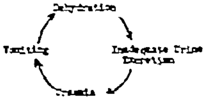

FIG. 3. Cycle of uremia

The average normal acid-base composition of plasma is shown in table 3. It is essential that plasma is used for the estimation of chloride as the red blood cells contain very little of this element and consequently the chloride content of whole blood is influenced markedly by the number of red blood cells present.

As the waste products of metabolism are mainly acidic in nature, it is important that adequate amounts of base are available to combine with and neutralize them. From table 3 it will be noted that sodium constitutes the largest portion of base, consequently the amount of sodium is mainly responsible for determining the quantities of anions present.

Electrolytes are small ions and so have a greater effect on osmotic pressure than the larger molecules such as protein. Therefore, the osmotic value of the extracellular fluid depends almost entirely on the amount of sodium present, and when this is increased fluid will be retained.

Changes in the bicarbonate content of the plasma are frequently observed but they are always secondary to changes in some other part of the electrolyte structure. For example, in prolonged vomiting more chloride than sodium is lost and so bicarbonate is retained to combine with the free sodium ions in the body, and the patient is said to be in alkalosis (table 4,a). If the vomiting continues and no food is ingested the patient develops ketosis from starvation, and the organic acids increase in the body fluids. These are neutralized by combining with sodium which is made available by dissociation from its combination with bicarbonate, and so the amount of this radical is reduced proportionately. Now the patient will exhibit ketonuria but the bicarbonate may still be elevated.

TABLE 3. *Ions in m/eq. concentrations normal plasma (1 litre)*

Cations (Base)		*Anions* (Acid)	
Na^+	142	Cl^-	103
K^+	5	HCO_3^-	28
Ca^+	5	$Protein^-$	16
Mg^+	3	PO_4^-	2
		SO_4^- & Organic	6
Total	155	Total	155

TABLE 4. *Electrolyte pattern in prolonged vomiting (m/eq. per litre)*

NORMAL		A. EARLY		B. WITH STARVATION KETOSIS	
		Content	Deviation	Content	Deviation
Total Base	155	149	−6	147	−8
Acids Cl^-	103	80	−23	78	−25
HCO_3^-	28	45	+17	37	+9
Organic	6	6	±0	14	+8
Others	18	18	±0	18	±0
Total	155	149	−6	147	−8

Because acid metabolites have been retained the patient is in acidosis in spite of the increased plasma bicarbonate level, and so this electrolyte alone may not accurately reflect the clinical state of the patient (table 4,b).

When retention of acid metabolites or phosphorus precedes the loss of chloride the plasma bicarbonate content falls to subnormal levels. As this is the more usual sequence in the initial stages of renal failure, the plasma bicarbonate estimation is valuable. Burnett et al have demonstrated that severe renal failure may accompany acute alkalosis and so the early detection and treatment of both acidotic and alkalotic states is of importance to the urologist.

The amount of isotonic sodium chloride required to restore the chloride content of a patient can be calculated from a knowledge of the total volume of the extracellular fluid (approximately 20 litres) and the plasma chloride deficiency (23 m.eq. per litre) (table 5). If treatment is based on the plasma chloride estimation alone, this patient will receive approximately 3 litres of isotonic NaCl. This will also supply approximately 330 m./eq. too much sodium and so to restore electrolyte equilibrium, the kidneys must excrete 330 m./eq. of the sodium supplied but retain all the chloride. In order to do this the urine output will have to increase markedly and consequently the dehydration will be increased and the final result will be a state similar to that seen in pure water loss (fig. 2). If the same amount of NaCl is administered as a hypertonic solution less water will be available for excretion of the excess sodium, more will be retained and the osmotic pressure of the extracellular fluid will increase, and "intracellular dehydration" and possibly edema will result. For these reasons it is never advisable to administer hypertonic solutions when treating dehydration, especially if the patient is complaining of thirst. Sodium chloride 0.9 per cent in water is an isotonic solution but 0.9 per cent sodium chloride in 5 per cent glucose in water is hypertonic and therefore should not be used. Glucose is required by practically all patients who need parenteral feeding and so it is advisable to administer an isotonic solution of glucose and saline, such as a mixture of ⅓ isotonic saline and ⅔ isotonic glucose.

TABLE 5. *Isotonic sodium chloride solution required (litres)*

	Normal	*Observed*	*Deficiency*
Plasma chloride m.eq./litre	103	80	23
Plasma sodium m.eq./litre	142	136	6

Total extracellular fluid = Approximately 20 litres.

$$\text{Isotonic NaCl solution} = 0.9\ \text{gm.}\ \% = 900\ \text{mg.}\ \% = \frac{900 \times 10 \times 1}{58.5}$$

$$= \underline{\text{Approximately 150 m.eq./litre.}}$$

Chloride deficiency in 1 litre extracellular fluid = 23 m.eq.
Chloride deficiency in 20 litre extracellular fluid = 460 m.eq.
Sodium deficiency in 1 litre extracellular fluid = 6 m.eq.
Sodium deficiency in 20 litre extracellular fluid = 120 m.eq.

$$\text{Amount isotonic NaCl to supply 460 m.eq. } Cl^- = \frac{460}{150} = \underline{\text{Approx. 3 litre}}$$

Excess Cl^- provided by 3 litres isotonic NaCl = Nil
Excess Na^+ provided by 3 litres isotonic NaCl = (150 × 3) − 120
= 330 m.eq.

It is also apparent that one cannot assume a deficiency in body sodium because a low plasma chloride level is detected. Much damage can follow the administration of large volumes of sodium chloride solutions in attempts to supply adequate amounts of chloride because such therapy may result in overloading the body with sodium. No other solutions containing chloride are as suitable for parenteral administration as the sodium salt and so it is necessary to evaluate the sodium content of the plasma if accurate replacement therapy is to be administered. The direct estimation of plasma sodium is technically difficult but as chloride and bicarbonate are the largest amount of acids (table 3) a reasonably accurate evaluation of sodium can be obtained from the more easily estimated plasma chloride and bicarbonate ions. The average normal chloride and bicarbonate content of the plasma totals 131 m/eq. *per litre (table* 6,a). It is reasonable to assume that these are combined with sodium, so if the estimated plasma chloride plus bicarbonate is less than 030 m.eq. per litre there will be a deficiency of similar amount in sodium (table 6). This assumption is not strictly accurate as will be seen from table 6,c, but ketonuria was present in this case and the retention of acid metabolites accounted for the discrepancy. Testing the urine for ketone bodies is a simple procedure which should never be omitted as ketonuria indicates not only that the patient requires to metabolize more glucose, but also that body sodium will be further depleted because these acids are partly excreted as sodium salts.

Estimation of the sodium deficiency by subtracting the observed values for plasma chloride and bicarbonate from 131 m/eq. does not replace the chemical evaluation of serum sodium, but when the latter test is impracticable this substitute will approximately define the amount of sodium present in the extracellular fluid. This will enable more accurate replacement therapy to be given and prevent the dangers which attend the administration of large excesses of sodium. In many cases the chlorides will remain deficient if only sufficient sodium chloride is administered to correct the sodium depletion, and so the clinician must decide whether or not the patient can excrete additional sodium before attempting to inject enough NaCl to restore the chloride to more normal levels. Most of the cases demonstrating a greater depletion of chloride than of sodium will also show a decrease in potassium concentration (table 6) and so if the urine output is adequate potassium chloride may be administered slowly.

TABLE 6. *Estimation of sodium deficiency from observed values of chloride & bicarbonate (m.eq. per litre)*

CLINICAL CONDITION	(A) NORMAL	(B) TABLE 4A	(C) TABLE 4B	(D) CHOLECYSTECTOMY	(E) PYLORIC OBSTN.	(F) RENAL ACIDOSIS
Cl^-	103	80	78	77	76	109
HCO_3^-	28	45	37	31	55	10
Total	131	125	115	108	131	119
Abnormality	±0	−6	−16	−23	±0	−12
Observed Na^+	142	137	135	118	141	133
Abnormality from:						
(1) Observed Na^+.	±0	−5	−7	−24	−1	−9
(2) Estimated anions	±0	−6	−16	−23	±0	−12
Serum potassium	*5.0*	*4.1*	*3.9*	*3.6*	*2.9*	*3.5*

It is equally important to determine the extent of sodium depletion before ordering M/6 sodium lactate and give less solution if it is considered that the patient will not be able to excrete excess sodium.

The clinical condition of the patient must be considered when deciding the amount of fluid which can be administered. It is always advisable to inspect the neck veins. If these are distended there is great danger of precipitating cardiac failure by intravenous therapy, and so fluid must be given slowly and only in small quantities.

If undue emphasis appears to have been placed on the role of sodium in the body fluids it is because sodium salts are most commonly administered parenterally but it is not intended to minimize the importance of other electrolytes. The true purpose of parenteral therapy is to replace losses as accurately as possible and so fluids and electrolytes must be administered with the same knowledge and precautions that attend other therapeutic measures. The intelligent interpretation of certain simple estimations on blood plasma and a knowledge of the fluid requirements of a patient give valuable information about the amount and type of fluid to administer as too much may have disastrous consequences and too little will not be effective. The kidney is the all-important regulating mechanism of the body and in the practice of urology we must remember that its ability to function normally may be impaired.

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LEIOMYOSARCOMA OF THE KIDNEY

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Leiomyosarcoma belongs to the group of very rare malignant kidney tumors. Because of its rare occurrence, it receives but scant attention in the average textbook. A careful review of the literature since 1929 reveals the reports only of 14 cases. Several hundred letters were sent to outstanding urologists. Replies were received from 50, none of whom had ever seen a patient with this condition.

Because of its rare occurrence, I wish to report the following case:

CASE REPORT

M. R., a white man aged 62 years, was admitted to the hospital on March 22, 1950. He was discharged April 5, 1950. An operation for a right inguinal hernia was performed several years ago. In 1946 he had a transurethral resection for benign prostatic obstruction from which he made an uneventful recovery. In December 1949, he experienced attacks of sharp intermittent pains in the right side of his abdomen. A diagnosis of duodenal ulcer was made and he was placed upon ulcer management with complete relief of pain. One week before admission to the hospital he had an attack of painless hematuria. The hematuria gradually diminished and the voided urine upon admission to the hospital was normal.

The physical examination was negative except for the presence of an enlarged mass in the right upper quadrant of the abdomen which was not tender and moved with respiration. The blood count and urinalysis were normal. The Kahn test was negative. The rectal examination was negative.

An excretory urogram showed that the left kidney was normal. The right kidney had a filling defect compatible with tumor.

Cystoscopic examination was negative. The urine from the right and left kidneys were free of pus, sterile upon culture, and negative on gram stains. The nonprotein nitrogen was 36 mg. per cent.

A right nephrectomy was done March 24, 1950 under pentothal sodium, nitrous oxide anesthesia. Delivery of the kidney was difficult because of adhesions. The twelfth rib was resected.

Microscopic diagnosis by Dr. George M. Hass: Leiomyosarcoma of the kidney with compression atrophy (fig. 1).

The patient made an uneventful convalescence. Recent examination on January 10, 1951 was negative.

DISCUSSION

A careful perusal of the literature since 1929 revealed the following reports of leiomyosarcoma of the kidney. Unfortunately many of the cases were reported

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 16, 1951.

* Deceased

in a very brief manner, as simple case reports, often lacking important details and but few carry any discussion of the subject.

Berry (1929). Female, 26. She first noticed pain in the right loin, and frequency of urination 14 months previously during the seventh month of her first pregnancy. After the child was born, symptoms continued. Exploratory operation revealed a leiomyosarcoma of the kidney involving the lower pole of the right kidney. Nephrectomy eight months later. Patient was still well two and one-half years later with no evidence of metastases.

Crosbie and Pinkerton (1932). Female, 35. She had moderate pain in the lumbar region with frequency of urination. Operation revealed a malignant leiomyoma of the kidney.

Swan (1933). Male, 71. Leiomyosarcoma of left kidney. Patient was still well 12 months after nephrectomy.

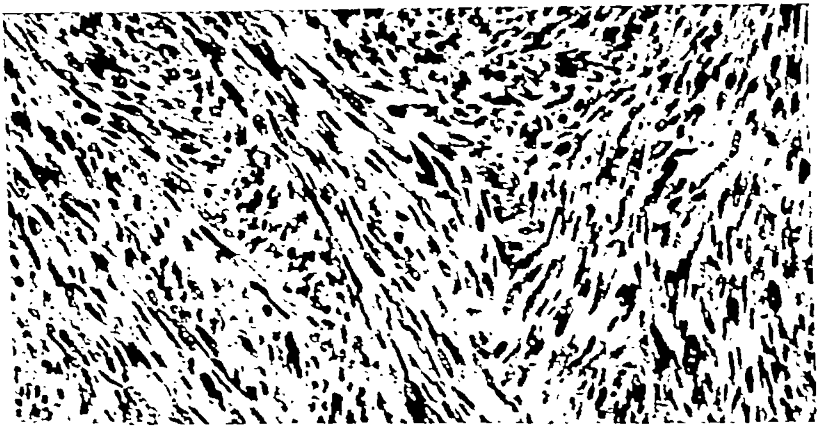

FIG. 1

Cooke (1933). Female, 60. During exploratory operation patient died. The autopsy showed a malignant leiomyoma of the kidney, with metastases to omentum, peritoneum, and liver.

Smith, G. G. (1935). In his series of 40 cases of tumor of the upper urinary tract which came to him for operation, there was one leiomyosarcoma of the kidney. The patient was alive and well 18 months after operation.

Patch (1937). Male, 55. He had pain in the right loin; passage of blood clots. Nephrectomy for malignant leiomyoma of the kidney with extension into the renal vein.

Mintz (1937). The records of the Massachusetts General Hospital revealed the following 4 cases of leiomyosarcoma of the kidney:

Female, 46. Pain and vomiting 3 weeks; palpable mass in right side. Operation. Lipoleiomyosarcoma of the kidney. Recovery.

Male, 37. Vomiting; urine red; abdominal mass. Exploratory operation at which diagnosis of polycystic disease was made. Death 5 days later. Author showed *bilateral* lipoleiomyosarcoma of the kidneys.

Female, 45. Pain in left back and lower left abdomen; frequency of urination;

palpable mass in left kidney region. Nephrectomy for leiomyosarcoma of left kidney. Patient died.

Female, 41. Pain in right groin and flank; movable mass in right upper quadrant. Right nephrectomy. Leiomyosarcoma. Patient recovered.

Tetelman and Lisa (1945). Autopsy findings in patients, aged 86 and 74. Leiomyosarcoma of the kidney.

Shaheen, Cassano and Lisa (1944). In 1923 cases of primary tumors of the kidney among 5,100 necropsies, there was only one case of a leiomyosarcoma. This tumor did not produce symptoms.

da Silva Horta and Madureira (1946). Male, 64. Grawitz tumor of the kidney with sarcomatous, leiomyomatous and chondromatous structure.

A review of the cases showed that the youngest patient was 26 years of age, and the oldest 86 years of age. Three cases occurred in the decade from 40 to 50 and three, including my case, occurred in the decade from 60 to 70. In one case reported by Mintz, the lesion was bilateral.

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RADICAL NEPHRECTOMY FOR NEOPLASM

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The behavior of malignant tumors wherever situated has dictated that surgical procedures for their removal be radical: extirpation of a peripheral segment of tissue along with neighboring lymph channels, lymph nodes, blood vessels and other structures to which the neoplasm may have extended even though there is no gross evidence of such extension.

The radical mastectomy of Halsted for breast cancer is an example of this well founded surgical thinking and plan of operation. High amputation for small bone lesions is another. Hinman's radical operation for testicular neoplasm removes the spermatic fasiculus, spermatic vessels, retroperitoneal fat, lymph nodes and lymph channels. Total gastrectomy for small malignant lesions of the stomach has vindicated itself. These examples are enough to point out the thesis of this communication, though other analogous examples are obvious without mention.

In dealing with malignant renal tumors the fundamental surgical principles of wide excision and removal of surrounding not grossly involved and apparently normal structures have not been followed. There have been some bizarre suggestions in this direction, such as opening the vena cava to extract from it neoplastic extensions into its lumen, which must be to no purpose. In a cursory way many writers have suggested that the perinephric fat be removed with the kidney, but make no suggestion as to how it should be done. The easy, simple and obvious removal of the immediately adjacent perinephric structures: the perinephric fat, renal fascial envelope, adrenal and vena cava from the renal veins downward to the bifurcation has never been urged. Most surgeons have been satisfied either to make the ordinary conservative nephrectomy with enucleation of the kidney from its surrounding fat or to remove also some of the perinephric fat by enucleation through the fat, but not including the pararenal fascia.

All urologic surgeons of much experience have well realized that in a large proportion of cases of nephrectomy for renal neoplasm, some or all of the surrounding structures have been invaded and that this ordinary form of nephrectomy inevitably leaves parts of the neoplasm behind.

This maldirection of surgical effort has persisted in face of the fact that almost no structure in the human anatomy, certainly no intra-abdominal organ, is better formed and related to surrounding structures than the kidney for easy radical removal along with all of the immediately surrounding structures to which the neoplasm may have extended.

All urologic surgeons of much experience have made nephrectomy for neoplasm only to find upon examining the removed kidney that the plane of enucleation between the capsule and perinephric fat or through the fat went through an area of extension of the parenchymal growth into the fat. Recurrence within a year or two has substantiated the misgiving at the time of operation and has been another addition to the poor results of ordinary nephrectomy for neoplasm.

Read at annual meeting, American Urological Association, Chicago, Ill. May 24, 1951.

Some years ago a new and radical form of nephrectomy for neoplasm was devised by one of us (F. E. B. F.) and has been in use by all of us.[1]

The preconceived form of operation was accurately planned, based on the behavior of renal tumors and on the anatomy of the kidney and its surrounding structures, particularly the renal fascia (O.T. fascia of Gerota).

On several occasions the mass of tissue: kidney, perinephric fat, fascial envelope and adrenal removed by the form of radical nephrectomy to be described, has been examined with the finding of extension of the parenchymal growth into the surrounding structures. If permanent cure has been achieved in these cases it is due to this form of operation and the avoidance of ordinary conservative nephrectomy.

Description and presentation of the new operation "Radical Nephrectomy for Neoplasm" at this time is prompted by a recent publication of Beare and McDonald[1] and the urging of the junior authors (W. P. M., E. J. R., and I. V.) who have felt the report should not await statistical study to determine the results it achieves.

For the purpose of determining the incidence of neoplastic invasion of the renal capsule and perinephric fat by hypernephroma, Beare and McDonald made detailed gross and histologic examinations of 488 surgically removed kidneys containing hypernephroma.

In 75 cases there was extension of the neoplasm to or into the renal capsule. In 268 cases the growth had gone beyond the renal capsule with invasion of the perinephric fat. In no case was neoplasm present in the fat without accompanying invasion of the renal capsule. It appeared, therefore, that involvement of perinephric fat occurs by direct extension and presumably does not occur by metastasis.

The above observations point out that among 488 cases of renal hypernephroma, the neoplasm had extended beyond the kidney in 343 cases, which is more than 70 per cent of the cases. From this observation, the substantial quality of the report and from impression gained from our own experience and observations, this appears to be a conservative estimate of the percentage of extrarenal direct extension in cases of renal hypernephroma subjected to nephrectomy.

Among the cases of renal capsule and perinephric fat involvement, Beare and McDonald found a smaller percentage of 5-year survivals than among the cases of neoplasms completely contained within the kidney.

The statistical findings of Beare and McDonald, substantiated by our clinical experience, also point out that from the standpoints of complete eradication of the neoplasm and permanent cure, the ordinary form of "conservative" nephrectomy, with enucleation through the perinephric fat, must be ineffective in 70 per cent of cases of renal hypernephroma. Both sets of observations give clear indications for "radical nephrectomy for malignant neoplasm" and good warrant for presenting in a published report the form of radical nephrectomy devised several years ago, as mentioned above, along with a sufficiently detailed description of the method to encourage its use by others and with a view to promoting its widespread adoption.

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[1] Beare, J. R. and McDonald, J. R.: Involvement of the renal capsule in surgically removed hypernephroma: A gross and histopathologic study. J. Urol., 61: 857–861, 1949.

Before proceeding with preparation of this report describing a form of radical nephrectomy for neoplasm, search of the literature was made to find expressions bearing on the subject and to determine whether or not a similar or identical plan of operation had been previously described. To this end we have referred to all publications from 1896 to date with titles suggestive of bearing on this phase of the matter. In these publications we have been unable to find any comprehensive consideration of the anatomic relationships on which a truly radical nephrectomy must be founded, no detailed suggestion for taking advantage of these relationships and no adequately planned and described method of operation.

However, the search did disclose a substantial number of vague comments on the importance of removing perinephric fat along with the kidney, but not even vague suggestion as to how this should be done.

In 1916, Kretschmer[2] advocated removal of the perinephric fat after nephrectomy for tuberculosis. In 1922, Fedoroff[3] reported having attempted to remove the perinephric tissue after nephrectomy for hypernephroma had been made. In the same year Stevens[4] advised complete removal of the kidney, perinephric fat, suprarenal capsule, lymph vessels and glands en masse, but presented no anatomic considerations bearing on the suggestion and described no plan of operation for its accomplishment. In 1926, Vivian[5] made a similar suggestion. In 1929, Judd and Hand[6] recommended early ligation of the renal vascular pedicle and removal of the capsule and as much perinephric tissue as possible, but did not present a plan of operation. Mathé[7] in 1945 concluded that it would be well to remove the entire perinephric fat in cases of tumor and in certain cases of renal tuberculosis. In 1948, Cahill[8] mentioned preliminary ligation of the vessels followed by removal of the kidney and perinephric fascia en masse. Cahill's mention of perinephric fascia removal is the only allusion we have been able to find to this anatomically and surgically important feature of the operation we have devised.

Chute[9] in 1949, in describing the value of thoraco-abdominal incision for removal of renal tumors, urged early ligation of the vessels and removal of the perinephric fat, lymph nodes and areolar tissue around the pedicle en bloc with the tumor.

Recently Sweetser[10] described a method of operation for renal neoplasm which

[2] Kretschmer, H. L. et al.: Surg., Gynec. & Obst., **23:** 391–395, 1916.

[3] Fedoroff, S. P.: Solid tumors of the kidney. Ztschr. f. Urol., **16:** 9, 1922.

[4] Stevens, W. E.: Diagnosis and treatment of malignant tumors of the kidney. J. Urol., **10:** 121–134, 1923.

[5] Vivian, C. S.: Hypernephroma. Southwest. Med., **10:** 7–9, 1926.

[6] Judd, E. S. and Hand, J. P.: Hypernephroma. J. Urol., **22:** 10–21, 1929.

[7] Mathé, C.: Evaluation of different types of nephrectomy; review of 247 cases. J. Urol., **53:** 85–91, 1945.

[8] Cahill, G.: Cancer of kidney, adrenal and testis. J.A.M.A., **138:** 357–362, 1948.

[9] Chute, R., Soutter, L. and Kerr, W. S., Jr.: Value of thoraco-abdominal incision in removal of kidney tumors. New Eng. J. Med., **241:** 951–960, 1949.

[10] Sweetser, T. H.: Surgery of retroperitoneal tumors. J. Urol., **57:** 651–659, 1947.

took into account the need for something more radical than the usual form of nephrectomy. The features of the plan were directed toward overcoming the technical difficulties of extraperitoneal removal of kidneys much enlarged by neoplasm, early ligation of the pedicle and removal of perinephric fat. Particular emphasis was placed upon the form of extraperitoneal incision: the usual oblique flank incision plus addition of a limb extending from its anterior extremity at the border of the rectus muscle upward to the level of the xiphoid process.

It is difficult to see that transperitoneal approach would add anything to the exposure and facility of this plan described by Sweetser. Sweetser recommended perinephric fat removal, but did not describe the anatomic considerations and dissection for its accomplishment.

In cases of lower pole tumor, the growth may have extended to and become adherent to the vena cava. Separation of the growth from the vena cava by either sharp or blunt dissection would be hazardous and to no purpose because of failure to accomplish complete extirpation. In most such cases it is possible to mobilize the vena cava above and below the segment of invasion and remove *this segment of vena cava en masse along with the renal mass.*

Ligation of the vena cava below the level of the renal veins may be made with relative impunity.

The first recorded ligation was made in an animal in 1669 and was fatal. Some of the earliest ligations of the vena cava were made incident to its injury during nephrectomy. Küster[11] in 1896 reported a case in which the inferior vena cava was injured and resected during nephrectomy. Death occurred 26 hours later. Pleasants[12] in a lengthy review of 8 cases of caval ligation or excision made previous to 1911 stated that death resulted in only two of the patients. All of these ligations were occasioned by caval injury during nephrectomy.

In the modern treatment of thrombo-embolic disease, ligation of the inferior vena cava has become commonplace. Rents and exploratory incisions in the vena cava made during nephrectomy by contemporary surgeons are commonly reported and dealt with by repair or ligation. Donovan[13] recently reported successful removal of a segment of vena cava measuring 1½ inches with a neoplasm of the right kidney. We have ligated the inferior vena cava in 8 cases of vesical neoplasm prior to extensive electro-excision and massive electrocoagulation of the tumors and have eliminated pulmonary embolism completely. Side effects have been transient and not disabling.[14]

Animal experiments are now in progress[15] which indicate that animals may survive ligation of the inferior vena cava above the level of the renal veins if preliminary ligation at a lower level is done to allow development of collateral circulation.

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[11] Küster, W.: Deutsche Chir., **3B:** 1614–1618, 1896–1902.

[12] Pleasants, J. H.: Obstruction of inferior vena cava with a report of eighteen cases. *Johns Hopkins Hosp. Rep.* **16:** 363–548, 1911.

[13] Donovan, H.: A malignant right kidney removal at operation together with a short length of vena cava. Brit. J. Urol., **17:** 107, 1945.

[14] Foley, F.E.B.: Urologists' Correspondence Club Letter, Feb. 1951.

[15] Lespinaise, V.: Ligation of vena cava above the renal veins with or without nephrectomy. Quart. Bull. Northwestern Univ. Med. Sch., **21:** 312–316, 1947.

In the light of these facts, removal of a section of vena cava in right nephrectomy for neoplasm may well become a part of a radical plan of operation.

RATIONALE OF RADICAL NEPHRECTOMY FOR RENAL NEOPLASM

The principle of radical wide excision of malignant neoplasm needs no special argument or vindication in the case of kidney tumors. The frequently appearing recommendation that "the perinephric fat should be removed with the kidney" indicates that in the surgical treatment of renal neoplasm there is vague agreement on the importance of this principle. But in none of the publications to which we have referred is adequate emphasis placed on the grave importance of this principle. Also we have been unable to find any detailed account of the anatomic considerations going with this principle and no description of a plan of operation or technique for its performance to make the principle truly effective. All of that is left vague.

As description of an operation to be performed, it is grossly insufficient merely to say that "the perinephric fat should be removed with the kidney." The surgeon, particularly the young and inexperienced surgeon, looking for information on this subject will find no benefit from that.

The literature and textbooks of urology abound in descriptions of the anatomic considerations, plans of operation and technique for their accomplishment in dealing with malignant neoplasm of other genito-urinary tract organs, particularly the testicle, prostate and bladder. So far as we have been able to determine, similar consideration has not been given to the anatomic considerations and surgical procedure for "radical" extirpation of malignant kidney tumors. Merely it is said that the nephrectomy should be accompanied by removal of the perinephric fat. Also it is sometimes pointed out that ligation of the renal vascular pedicle should be made early in the procedure before the kidney itself is disturbed and handled with the possibility of thus effecting dissemination. It has appeared to most writers that this latter desirable feature of the procedure is best accomplished by transperitoneal nephrectomy. We cannot share this view and will point out that by taking proper advantage of the anatomic relationships and following a well planned dissection, early ligation of the pedicle can be made as part of an extraperitoneal nephrectomy with no prior disturbance or handling of the kidney, with even greater facility and ease than it is accomplished by transperitoneal operation.

Description of a well perfected and long practiced technique of operation which accomplishes radical wide excision of the tumor-containing kidney is the main burden of this paper.

ANATOMIC CONSIDERATIONS AND TECHNIQUE OF RADICAL NEPHRECTOMY

The kidney, adrenal, upper part of the ureter, first portion of the renal lymph channels, adjacent lymph nodes, perinephric fat and vascular attachments of these structures and the spermatic (or ovarian) blood vessels are all contained in a fascial envelope which walls them off from surrounding structures. The fascial envelope is readily separable from surrounding structures in clean cleavage planes permitting it to be removed intact along with its contents en masse.

The fascial envelope referred to above is formed by the anterior and posterior layers of the renal fascia (O.T. fascia of Gerota).

It will be clear from careful reference to the masterly Max Brödel illustration (figs. 1 and 2) that the renal fascial envelope contains all of the structures needing removal to promise cure. Any neoplasm which has extended beyond these fascial planes is hopeless. In our opinion a tumor which has extended beyond the renal capsule, but is still confined within these fascial planes may be completely extirpated according to the method here described with some promise of permanent cure.

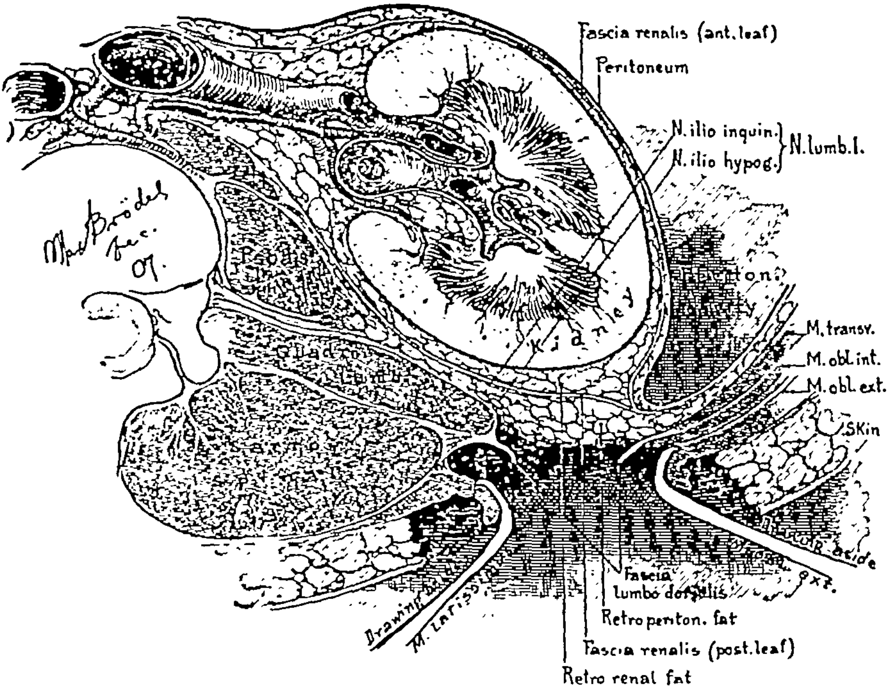

FIG. 1. Kidney, perinephric fat and renal blood vessels are completely enclosed in a fascial envelope formed by the anterior and posterior leaves of the fascia renalis (O.T. fascia of Gerota). Horizontal section.

There is a clean cleavage plane between anterior leaf of fascia renalis and peritoneum and a similar cleavage plane between posterior leaf of fascia renalis and muscles of renal fossa. Kidney with its surrounding fat and fascial envelope may be completely separated from surrounding structures by blunt opening of these cleavage planes. (Kelly and Burnam: *Diseases of the Kidneys, Ureters and Bladder*, New York: D. Appleton Company, 1922, vol. I.)

In the radical nephrectomy here described and properly performed, particularly if there is normally abundant fat surrounding the kidney, the surgeon never sees the kidney any more than he sees the "cancer" in a properly made mastectomy for carcinoma of the breast.

The plan of operation is based on the fact that both the anterior and posterior leaves of the renal fascia are readily separable from the structures against which they lie, with the same ease and facility with which the tunica vaginalis is separated from the dartos in excising a hydrocele. But if the operation is to be made as proposed and is to accomplish the radical en masse removal contemplated, there must be strict adherence to its anatomic plan.

METHOD OF OPERATION

Position of the patient is probably the most important technical detail of any kidney operation. Without proper position the procedure will be much impaired and beset by difficulties which may even defeat the plan of operation. The shoulder girdle and spine should be rotated forward away from the flank on the side of operation. This enlarges the space between the twelfth rib and crest of the ilium. Maximal lateral flexion of the spine is effected by the kidney elevator of the operating table and contributes most to opening the "costal-iliac" space.

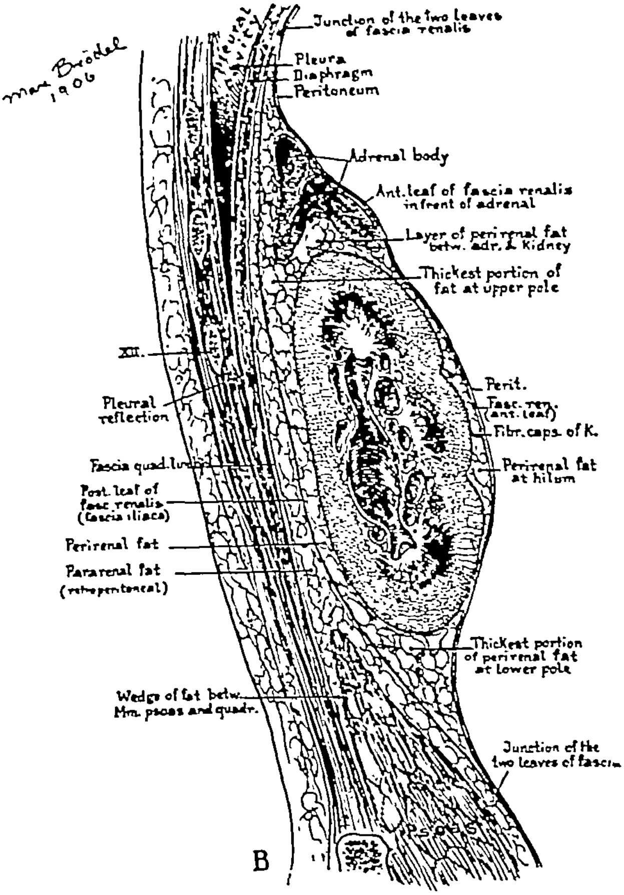
Max Brödel 1906
Junction of the two leaves of fascia renalis
Pleura
Diaphragm
Peritoneum
Adrenal body
Ant. leaf of fascia renalis in front of adrenal
Layer of perirenal fat betw. adr. & kidney
Thickest portion of fat at upper pole
XII.
Pleural reflection
Perit.
Fasc. ren. (ant. leaf)
Fibr. caps. of K.
Fascia quad. lumb.
Perirenal fat at hilum
Post. leaf of fasc. renalis (fascia iliaca)
Perirenal fat
Pararenal fat (retroperitoneal)
Thickest portion of perirenal fat at lower pole
Wedge of fat betw. Mm. psoas and quadr.
Junction of the two leaves of fascia
Psoas
B

FIG. 2. Relationships of kidney, perinephric fat, adrenal and fascia renalis to surrounding structures are shown in sagittal section. (Kelly and Burnam: *Diseases of the Kidneys, Ureters and Bladder*. New York: D. Appleton Company, 1922, vol. 1.)

A generous incision is a prime requirement. Such a procedure must not be handicapped by insufficient room and inadequate exposure. Beginning close to the spinous process of the tenth thoracic vertebra the incision is extended obliquely downward across the eleventh and twelfth ribs and is continued forward below and parallel to them obliquely across the abdomen to the edge of the rectus muscle. The latissimus dorsi, external oblique and internal oblique muscles are divided in the line of incision exposing the lumbodorsal fascia. The latter is split parallel to its fibers with exposure of the underlying posterior leaf of the renal fascia (fig. 3). The peritoneum is stripped away from the undersurface of the transversalis muscle medialwards to the sheath of the rectus muscle. The split in the lumbodorsal fascia is continued forward in the transversalis muscle medialwards to the sheath of the rectus. With the peritoneum freed from the undersurface of the transversalis muscle the fibers of the transversalis may be widely retracted. In the anterior part of the incision the perietal paritoneum now forms the floor of the wound cavity.

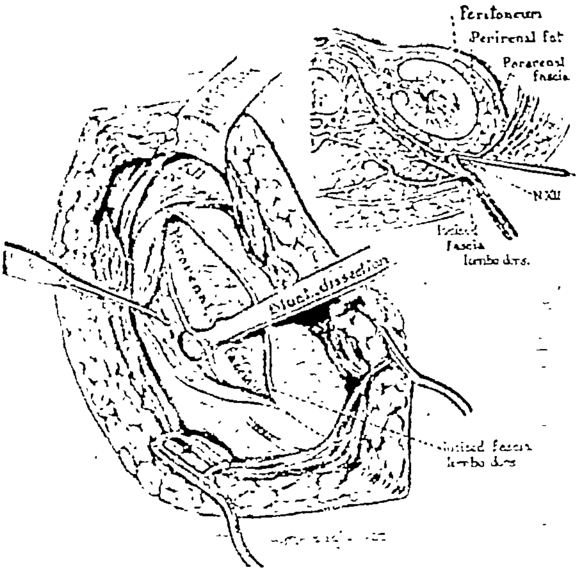

FIG. 3. Lumbodorsal fascia has been incised parallel to its fibers exposing pararenal fascia (fascia renalis). Beginning of blunt opening of cleavage plane between this fascia and muscles on which it lies is shown.

Next step will be blunt opening of cleavage plane between peritoneum and anterior layer of pararenal fascia (fascia renalis). Muscles covering costovertebral angle and costovertebral ligament will be divided giving wide exposure. (Foley: New methods for exposure of the kidney and nephropexy. Arch. Surg., 18: 1413–1426, 1929.)

The deep structures in the posterior angle of the incision are now divided: latissimus dorsi muscle, lumbodorsal fascia, costovertebral ligament, and, if need be, the edges of the quadratus lumborum and sacrospinalis muscles. Forceful upward retraction of the twelfth rib usually fractures it close to the vertebra and gives added room. If necessary, the twelfth, and additional ribs, may be removed to give the needed exposure, but is rarely required. In the posterior part of the incision the posterior leaf of the renal fascia forms the floor of the wound cavity.

The procedure thus far has exposed a considerable posterolateral area of fascial envelope containing the kidney and its immediately surrounding structures to be removed with it.

At the lateral border of the kidney, the parietal peritoneum, already separated from the transversalis muscle, passes from the abdominal wall to the anterior surface of the kidney from which it is separated by the anterior leaf of renal fascia and perinephric fat. At this point the cleavage plane between the peritoneum and the anterior leaf of the renal fascia must be accurately identified. If need be, a small opening is made in the peritoneum to permit pulling away this single layer from the underlying renal fascia. Once this cleavage plane is entered, the peritoneum is peeled away from the renal fascia by blunt dissection medialwards over the anterior surface of the kidney to the vertebral bodies. Blunt opening of the cleavage plane is continued upward and downward thus exposing the fascial envelope covering the fat over the anterior surface of the adrenal, kidney and ureter.

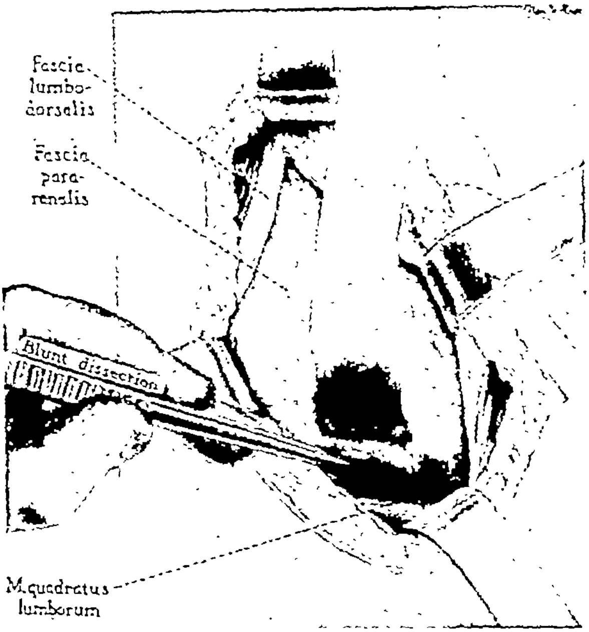

FIG. 4. Blunt separation of posterior layer of pararenal fascia (fascia renalis) from muscles of posterior abdominal wall is continued medialwards to vertebral bodies. (Foley, F. E. B.: Management of ureteral stone. J. A. M. A., 104: 1314–1317, 1935.)

With the parietal peritoneum, mesocolon and peritoneum-confined loops of bowel held medialwards, the anterior surface of the renal vascular pedicle should now be readily accessible for ligation. Or ligation may be postponed until the fascial envelope and its contents have been completely mobilized by separating the posterior leaf of the renal fascia from the muscles of the posterior abdominal wall, diaphragm and vertebral bodies.

Starting again at the lateral border of the kidney, the kidney and perinephric fat covered by the posterior leaf of the renal fascia are retracted forward. The areolar tissue traversing the cleavage plane between the renal fascia and quadratus lumborum muscle will be put on the stretch and divided by blunt dissection (fig. 4). Continuing the blunt dissection medialwards and downwards the renal fascia is separated from the quadratus lumborum, iliopsoas and finally from the vertebral bodies along which the vena cava is exposed. Blunt opening of this cleavage plane is continued downward behind the ureter, which is separated from the muscles behind it along with the peri-ureteral fat.

Continuing the blunt dissection upward the renal fascia separates from the diaphragm upward beyond the upper pole of the kidney. Above the upper pole of the kidney is a tent-like extension of the fused anterior and posterior leaves of the renal fasciae in which the adrenal is contained. The upward attachments of this tent of fascia may be more dense than to permit blunt separation and may require division with the scissors or scalpel.

Finally the whole renal fascial envelope with its contained kidney and other structures has been completely mobilized and is ready for removal (fig. 5). Both anterior and posterior leaves of the renal fascia, where they cross the vertebral bodies, are very thin and will have been broken through leaving only the vascular pedicle and ureter as attachments.

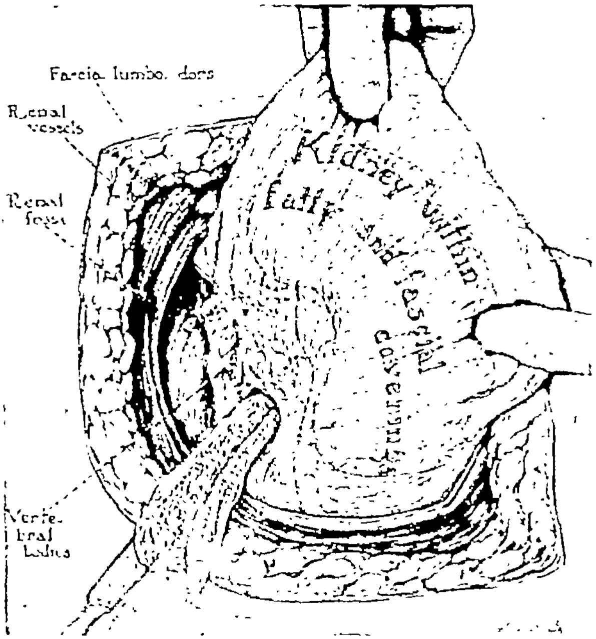

FIG. 5. Peritoneum has been separated from anterior layer of pararenal fascia (fascia renalis). Posterior layer of pararenal fascia (fascia renalis) has been separated from quadratus lumborum and iliopsoas muscles and lateral aspect of vertebral bodies medialwards almost to midline. Kidney enclosed in its fascial envelope and surrounding perinephric fat has been completely mobilized without kidney or its neoplasm having been uncovered. The plane of dissection has been peripheral to neoplasm. (Foley, F. E. B.: New methods for exposure of the kidney and nephropexy. Arch. Surg., **18**: 1413–1426, 1929.)

If the vascular pedicle was not ligated when first exposed by separating the peritoneum from the anterior leaf of the renal fascia, it is now doubly clamped and divided. The cut pedicle is twice ligated, with release of the proximal clamp as the first ligature is tied and release of the distal clamp as the second ligature is tied.

Now the only remaining attachments are the ureter and spermatic (or ovarian) vein (fig. 6).

The spermatic vein is divided and ligated followed by division and ligation of the ureter.

If the renal tumor is not extensive, or is not located in the upper pole of the kidney, the adrenal need not be removed. In that case, the tent of renal fascia containing the adrenal is incised or bluntly divided along the line of renal-adrenal junction and the adrenal is separated from the kidney and left in place.

The attachments of a lower pole tumor to the vena cava should not be disturbed. This segment of cava is excised between ligatures, one placed immediately below the renal vein, the other above the iliac bifurcation. The portion of cava attached to the lower pole neoplasm is excised with the mass. The ureter is then doubly clamped, divided and ligated completing the radical nephrectomy.

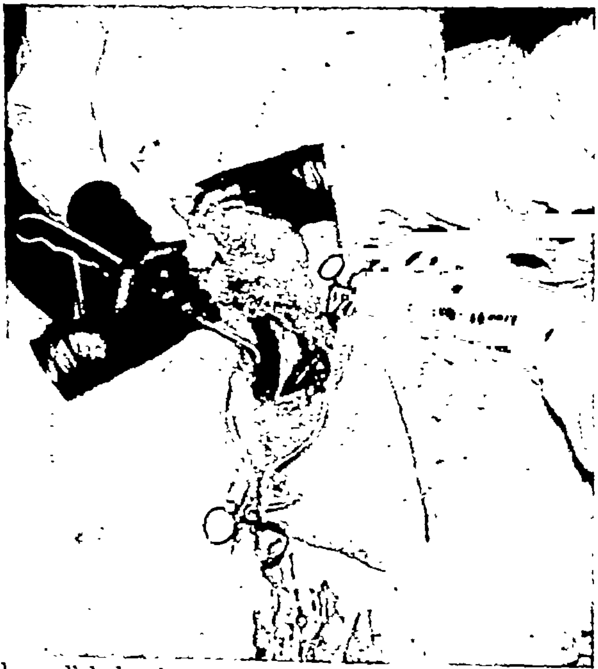

FIG. 6. Vascular pedicle has been divided and ligated. Tumor containing kidney, completely encased in its surrounding fat and fascial envelope, is held up out of wound in right hand of operator. Ureter and its surrounding fat are only remaining attachments. (Photograph at operation: Right radical nephrectomy for neoplasm.)

The nephrectomy has been made giving the kidney and its contained neoplasm the widest possible berth. The kidney itself has not been exposed and is completely surrounded by perinephric fat, the latter and the adrenal being contained in the fascial envelope.

In the particular case in which the photographs illustrating this presentation were made, it was apparent when the removed kidney was shelled out of its fat that the lower pole neoplasm had extended beyond the capsule into the fat and that ordinary nephrectomy with enucleation in the cleavage plane between the capsule and fat would not have completely extirpated the neoplasm.

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RENAL OSSIFICATION: REPORT OF OCCURRENCE IN AN APLASTIC KIDNEY

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Occasionally and under special circumstances, bone arises within tissues not connected with the osseous system and from connective tissue not ordinarily manifesting osteogenic potencies. When this occurs, the process is, therefore, not related to the formation of bone occurring in teratomas or in mixed tumors or resulting from embryonal transposition and segregation of bony cells in extraskeletal tissues because in all these conditions bone is formed from the specific activity of osteogenic cells.

"Metaplastic ossification" has been described in diverse locations and under a variety of experimental conditions.[1] From this it may be inferred that the connective tissue, as a whole, has latent osteogenic potencies and that periostea and perichondria merely exhibit to a special degree this universal transformability of the fibroblast.

At least two factors, one local and the other humoral, seem to be essential to activate this latent potency. The humoral factor is related to the supply of minerals in the fluids of the body, and to the solubility of the calcium and phosphate salts. The local factor determining the deposition of the bone salt is not as yet clearly understood. A fact is, however, apparent: that certain organs and tissues create more often than others the conditions necessary for the occurrence of the phenomenon. Aside from the skeletal system, this seems to be the case of the urinary tract which numerous experiments have proven to be a fertile ground for "metaplastic" formation of bone.

As far back as 1880, Litten[2] demonstrated the possibility of producing extensive calcification of the kidney of rabbits by temporary interruption of the renal blood flow. Using the same animal and experimental approach, but making the ligature of the artery permanent and complete, Sacerdotti and Frattin (1901)[3] showed the formation of osteoblasts within the calcified areas, resulting within three to four months in the production of bone provided with bone marrow. Examination of the kidneys at successive intervals showed the gradual transition from the fibroblast to the osteoblast and formation of mature bone. More recently Ceccarelli (1931)[4] revealed that calcification and bone formation could be considerably accelerated when the ligature of the renal vascular peduncle was pre-

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This study was aided by the Lydia Raymond Research and Publication Fund of the Framingham Union Hospital.

Presented by Dr. Holtham, November 2, 1950, at a meeting of the New England Section, American Urological Association, Boston City Hospital, Boston, Mass.

[1] Maximow and Bloom. *Textbook of Histology, Philadelphia: W. B. Saunders Co.*, 1949, pp. 148-149.

[2] Litten, M.: Quoted by Sacerdotti and Frattin.[3]

[3] Sacerdotti, C. and Frattin, G.: Giornale della R. Academia di Medicina di Torino 7: 825-836, 1901.

[4] Ceccarelli, G.: Arch. ital. di Urol., 7: 614-624, 1931.

ceded from 20 to 50 days by the ligature of the corresponding ureter, 2 cm. below the pelvis. That the deposition of calcium salts is not the factor underlying renal ossification was shown, however, by Asami and Dock (1920)[5], who following ligature of the vascular peduncle noticed formation of bone, independently from calcification in the loose vascular connective tissue lying beneath the transitional epithelium of the calyces.

The existence in the urinary tract of a factor predisposing to metaplastic ossification is further shown by the experiment of Strauss (1914)[6], who following the application of pedunculated flaps of fascia in the walls of the ureters of dogs, in every instance noticed formation of a layer of bone bordering the lumen of the ureter and converting it into a rigid tube. Grafts of fascia lata in the walls of the urinary bladder similarly were followed by formation of bone (Newhof, 1917).[7] Calcification was seen to begin 6 days and ossification, 17 days after application of the graft.

In the light of these conclusive experiments one would expect to find frequent reports of bone formation in the kidney under spontaneous pathological states, mainly those implying interference with blood flow and secretion output. To judge from the scarcity of reported cases, spontaneous formation of bone in the urinary tract is instead a rare condition. Nine such cases, including one of his own, were presented by Severi in 1942.[8] The first mention of metaplastic bone formation in the kidney is attributed by Severi to Kroenlein (reference and date not given),[9] who described islands of bone formation in the walls of a large polycystic kidney. It was also in a polycystic kidney that Andrei[10] noticed bony structures. Cartilage, not bone, was present in the 2 cases of polycystic kidney described by Luzzatto.[11] In the case of DeFaria and Fialbo[12] and in the similar one reported by Rigano-Irrera[13] the bone was imbedded in the wall of a solitary renal cyst. In Severi's case bone was found in the walls of a hydronephrotic kidney. A condition of hydronephrosis was present also in the case of Lozzi,[14] in which bone was found within an impacted stone. Similarly, Phemister[15] described 2 cases in which living bone containing marrow, fat, loose fibrous tissue and blood capillaries was detected in the nucleus of stones in the renal pelvis. In both of these cases, the stones were being absorbed by fibroblasts and directly replaced by bone.

Reviewing the literature on aplastic and hypoplastic kidneys, 2 cases only were found showing clacification or bone formation. In the case of Hawes (1939)[16] calcified plaques, including bone, were noticed in the walls of a cystic hypoplastic kidney displaying imperfectly developed glomeruli and duct-like structures.

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[5] Asami, G. and Dock, W.: J. Exper. Med., **32:** 745–766. 1920.
[6] Strauss, A. A.: Surg., Gynec. and Obst., **18:** 78–84, 1914.
[7] Neuhof, H.: Surg., Gynec. and Obst., **24:** 383–427, 1917.
[8] Severi, A.: Arch. ital. di Urol., **19:** 147–158, 1942.
[9] Kroenlein: Quoted by Severi[5]
[10] Andrei, O.: Arch. ital. di Urol., **3:** 345–351, 1926.
[11] Luzzatto: Quoted by Severi.[8]
[12] DeFaria, G. and Fialbo, A.: Hospital, Rio de Janeiro, **14:** 241–254, 1938.
[13] Rigano-Irrera: Arch. ital. di Urol., **3:** 113–128, 1926.
[14] Lozzi, V.: Quoted by Severi[5]
[15] Phemister, D. B.: Ann. Surg., **78:** 239–249, 1923.
[16] Hawes, G. A.: J. Urol., **42:** 500–506, 1939.

Harrison and Botsford (1946)[17] reported a cystic, hypoplastic, nonfunctioning kidney which had undergone calcification. The ureter had developed only a distance of 4 cm. from the bladder. The x-ray findings were very similar to those in our case. No mention was made, however, of bone formation.

Comparable findings were observed in animals. Eustrongylos infestation of the renal pelvis is known to be a relatively frequent cause of hydronephrosis in a variety of animals. Under these conditions, metaplastic bone formation has been seen to occur. Bone tissue was found by Pasqua[18] in a calculus hydronephrotic kidney of a cow. Metaplastic bone in the pelvis of an ox, with extensive pyelonephrosis and a bladder tumor, is reported by Ronca;[19] since cartilage was also present, this author thought that the formation of bone had been preceded by a chondroid stage.

The report here presented adds to this meagre list of cases an instance of metaplastic formation of bone in a cystic, aplastic, nonfunctioning kidney.

CASE REPORT

A 25 year old graduate nurse was first admitted to another hospital on December 28, 1948 with the complaint of burning sensation and frequency in urination, gradually increasing in severity. Her family history was noncontributory and her past history was essentially negative, except for the usual diseases of childhood and for a right inguinal hernia repaired in 1944. During World War II she served as an Army nurse.

Physical examination at that time had disclosed tenderness in the right costovertebral region and no other significant findings. Blood pressure was 126 over 70. A catheterized urine specimen showed the sediment to be loaded with white blood cells and on culture, E. coli was obtained; no acid-fast bacilli were shown. The nonprotein nitrogen was 23 mg. per cent; the blood calcium 9.5 mg. per cent. An intravenous pyelogram showed a large circular, calcified shadow and a subjacent, smaller, rounded shadow in the left upper abdominal quadrant (fig. 1). No dye was excreted in the region of the left kidney. The right kidney showed slight dilatation and blunting of the calyces but the ureters and bladder were normal. A cystoscopy and right regrograde pyelography showed slight congestion of the bladder mucosa about the right ureteral orifice which, however, could be probed without difficulty. No note was made about the presence or absence of the left ureteral orifice. The urinary infection cleared up with combisul and streptomycin therapy. The diagnosis on discharge was acute cystitis and right pyelonephritis with nonfunctioning left kidney, and question of tuberculous autonephrectomy.

In 1949, the patient had two subsequent similar attacks and it was during the second attack that she was first seen by one of us (Holtham). At no time did she complain of any symptoms referable to the left kidney pelvis. A cystoscopy and retrograde pyelography showed the bladder to be moderately inflamed. A 5F ureteral catheter was passed with ease to the right renal pelvis. The left ureteral orifice was identified also and a No. 5 catheter passed into the corresponding ureter for a distance of 8 cm., but no urinary drainage was obtained and no dye was seen in the ureterogram beyond the tip of the catheter. The urine sediment showed 90–100 pus cells per high field magnification. No acid fast bacilli could be shown and guinea pig inoculation was negative after 6 weeks.

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[17] Harrison, J. H. and Botsford, T. W.: J. Urol., 55: 309–322, 1946.
[18] Pasqua: Quoted by Severi.[8]
[19] Ronca: Quoted by Severi.[8]

When the urinary infection had cleared up, a left nephrectomy was done (Holtham). The kidney was normally located but reduced in size and it was surrounded by thin fibrous adhesions. The capsule was smooth, glistening and calcified throughout and had a dense egg-shell like consistency. A firm, calcified nodule, 2.5 cm. in diameter, was attached by a cord of fibrous tissue extending from the hilum to several centimeters below the lower pole of the kidney. The ureter could not be identified to a distance of 15 cm. below the kidney. The renal pedicle was normally located but the vessels were very small and atrophic. The wall of the renal artery was thickened. The left adrenal was normal.

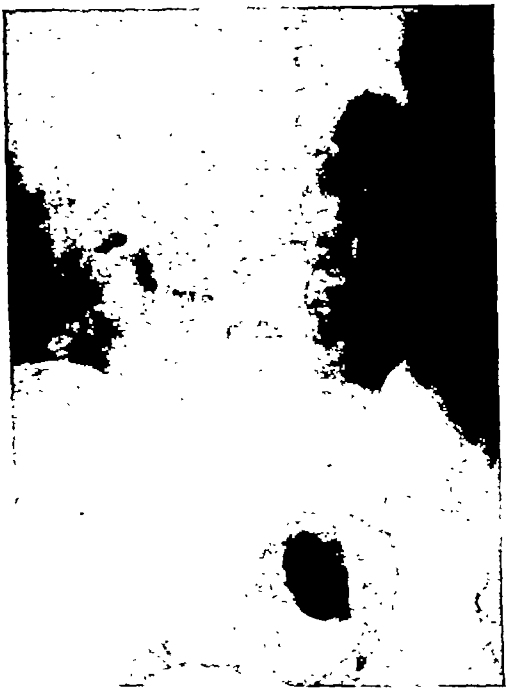

FIG. 1. Retrograde pyelogram showing normal right kidney and large calcified shadow with a second smaller calcified area in left renal fossa. Left ureterogram visualizes only lower third of left ureter.

Convalescence was uneventful and the patient left the hospital on the tenth postoperative day. She has been well and symptom-free since the operation.

Pathological examination of the removed specimen showed it to consist of a bean-shaped, shell-like formation, 8.5 cm. long and 5.4 cm. in width at the largest portion. Except for a number of fibrous attachments, it was smooth on the outer aspect and it displayed a homogeneous, pale gray color. On palpation, it was firm and nonfluctuant and found to be a single cyst that contained a cloudy grayish yellow fluid, and was lined by slightly roughened, pale gray surfaces. The walls of this cystic formation ranged in thickness from 0.2 to 0.3 cm. and showed widespread, irregularly distributed areas of dense calcification. At the lower pole of the formation there was a 1.5 cm. broad band of fibrous tissue which, upon dissection, displayed the presence of a 1.2 cm. long and 0.3 cm. thick tubular tract with pinpoint lumen and calcified walls. It was suggestive of a rudimental and almost completely obliterated vascular channel, probably the renal artery. No ureter could be detected. A smaller, irregularly rounded, ossified cystic mass was attached to this fibrous band. It measured 2.5 cm. across and both externally and on the cut section it showed a number of small lacunar spaces with a glistening lining and no solid or fluid content (fig. 2).

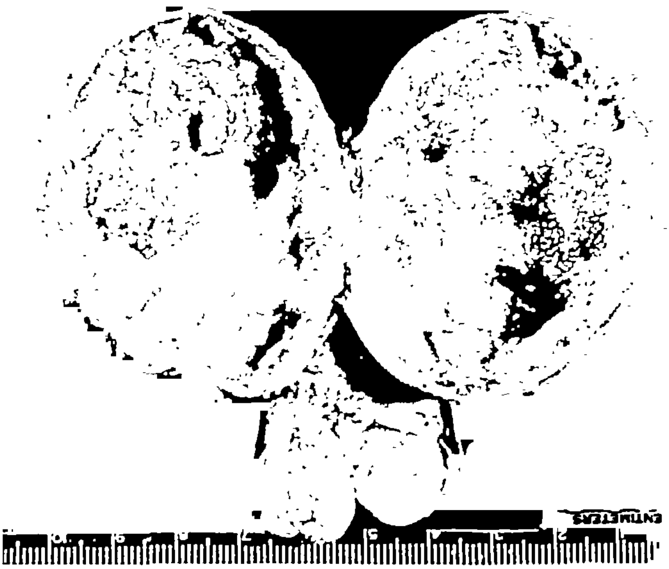

FIG. 2. Cross section of same kidney showing two adjacent cystic masses and intervening fibrous band including rudimentary renal artery.

The microscopic study of the larger cyst showed it to consist of fibrous connective tissue, poor in cells and in blood vessels. The former were mostly fibroblasts and cells with characteristics of histiocytes. This connective tissue was sclerotic in places and showed patchy calcification. Independently from the lime salt deposits, spongy bone was noticeable in broad areas. It consisted of irregular plates and bars of various thickness which branched and united with each other. The spaces between the plates were filled with vascularized connective tissue and with myeloid tissue, well-differentiated along all series (fig. 3, A). Numerous osteocytes were imbedded in the interstitial bone substance and regularly aligned osteoblasts were noticeable here and there at the edges of the bony plates. No differentiated renal elements or structures that could be identified as embryonal renal elements could be seen in any of the sections from the larger cystic mass. A few embryonal renal tubules were recognized, however, in the sections from the

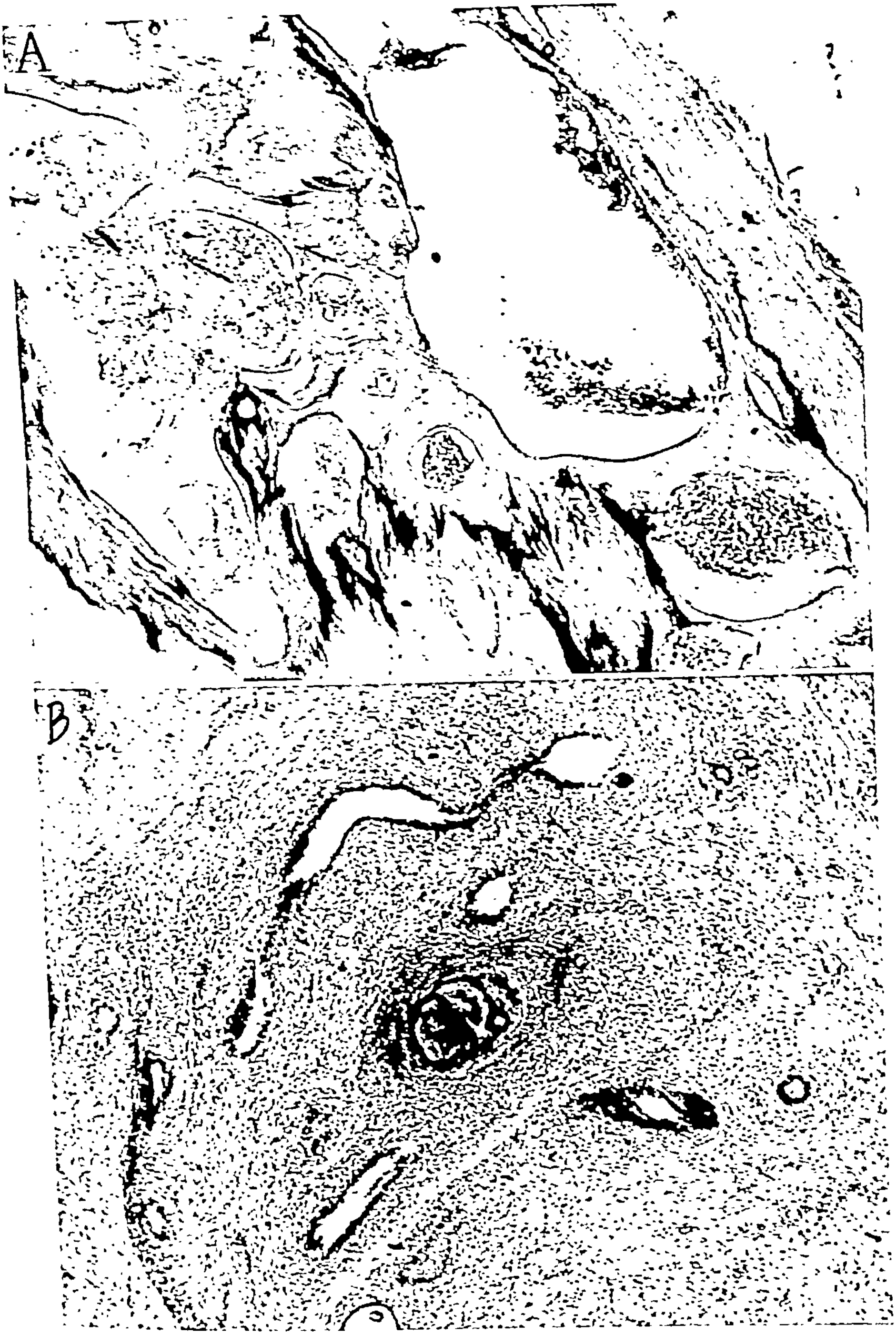

FIG. 3. *A*, irregular plates and bars of bone, branching and uniting with each other in walls of larger cyst. Spaces between plates are filled with loose fibrous connective tissue and with myeloid tissue, well differentiated along all series. *B*, rudimentary renal tubules, occasionally dilated to cystic dimension in wall of smaller cyst. Large size artery with calcified wall, lumen occupied by partially calcified thrombus and pronounced perivascular lymphatic infiltration, is noticeable in central portion of section.

smaller cyst (fig. 3, *B*). These tubules were imbedded in a fibrous connective tissue, ossified and calcified in places and poor both in cells and in blood vessels. They were irregularly distributed, far apart from one another, some were small and some others dilated, so as to give rise to microscopic cysts. The lining epithelium was deeply stained and ranged in shape from low cuboidal in the small tubules to flattened in the larger ones. No glomeruli were seen. The vascular tract recognized grossly and thought to be the rudimentary renal artery displayed on the sections widespread calcification of the walls and concentric intimal proliferation, resulting in almost complete obliteration of the lumen.

COMMENT

The term "renal aplasia" is generally used to indicate an incompletely or defectively developed kidney without a functioning drainage system; the term "renal agenesis" to indicate the absence of any vestige of renal tissue (Nation).[20] This being the situation, the presence of incomplete and defective renal structures in the formation under consideration ascribes our case to the category of the "aplastic kidneys." This condition is said to result from failure of proper union between the ureteral bud and the metanephros. The ureteral bud forms from the wolffian duct, near its cloacal end; soon afterward the major calyces are developed by slight cleavage of the dilated pelvic end of the ureter. Subsequently, several divisions occur until the entire collecting tubule system is formed. Each of these units is surrounded by a mass of nephrogenic tissue. The differentiation of this tissue into glomeruli and convoluted tubules occurs only after the collecting tubule system is formed. If the development of the Wolffian duct is impeded so that the ureter fails to develop, renal agenesis occurs. Another possibility is that the ureter is formed but fails to come in contact with the metanephron, or that either the ureter or the system of the collecting tubules or both do not develop properly or make proper connection with the nephrogenic tissue. In this case, tubular differentiation does not occur, the whole resulting in an aplastic kidney.

The findings in our case well substantiate the possibility that the renal aplasia resulted from failure of the ureter to join the metanephron during embryonal development. The unusual feature of the case here presented, however, is the formation of living bone, provided with bone marrow, in this defectively developed kidney.

The influence under which ordinary connective tissue gives rise to bone in the embryo are little understood, although it is clear that previously undifferentiated connective tissue cells are capable of developing into bony cells. It is also clear that once cells have exhibited osteogenic potencies, these potencies are readily evoked for an undetermined period after the cells have returned to an indifferent morphologic state. The formation of new bone from the fibrous periosteum and of cartilage from the pericondrum are instances of physiological metaplasia. The reverse transformation of osteoblasts to fibroblasts is illustrated by osteitis fibrosa and by a number of related pathological states characterized by replacement of bone by fibrous tissue. In all these conditions, the fibrous tissue results from the transformation of bone cells into fibrocytes, which again become functioning osteoblasts when re-ossification of the fibrous tissue takes place. This justifies the generally accepted conclusion that skeletal fibroblasts, chondroblasts, osteoblasts and osteoclasts must not be looked upon as distinct and immutable cell types but as interchangeable cellular elements. The formation of bone in our aplastic kidney is another example of the universal osteogenic potency of the fibroblast.

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[20] Nation, E. F.: J. Urol., 51: 579-586, 1944.

Early students of metaplastic ossification expressed the view that prerequisite to the phenomenon is the proliferation of the fibroblast. So does Virchow[21] in his book on new growths where he describes formation of bone within the brain matter in areas of fibroblastic cell proliferation resulting from "chronic encephalitis" and in the choroid membrane of the eye in cases of "chronic choroiditis." Lime-salt precipitation has also been advocated as another predisposing factor (Litten,[2] Kossa,[22] Lubarsch[23]), but against the assumption that calcification must necessarily precede ossification is the frequent demonstration of long standing lime salt deposits in organs and tissues, not accompanied by any formation of bone. On the other hand, it has been shown (Asami and Dock)[5] that ossification can occur independently from calcification and it is now well accepted that the property of calcifiability is conferred upon the transformed connective tissue by the osteoblast itself.

Pathologic calcification is generally considered to be either dystrophic or metastatic in nature. Metastatic calcification is associated with increased availability of calcium. Dystrophic calcification, by far the more frequent, may proceed without variation of the physiologic levels of any of the chemical constituent of the blood. As Wells[24] has stated "any area of dead tissue that is not infected and that is so large or so situated that it cannot be absorbed, will probably become infiltrated with lime salts." The enzymic degradation of tissues, with their content of nucleotides, phospholipids and phosphoric esters, results in a local excess of phosphate which may easily cause the calcium to precipitate from its physiologic levels. Inasmuch as the chemical bulk of both calcium and bone deposits consists of the insoluble form of tricalcium phosphate it is apparent that the relation of calcium to phosphate is of prime importance to the occurrence of either calcification or ossification.

The question was brought up by Phemister[15] as to whether there exists in the urinary tract a common factor which influences calcification, ossification and stone formation. Accepting the belief that both ossification and calcification generally occur in tissues that have an excess of acid present, Strauss[6] attributed the ossification in fascial flaps used to reconstruct the ureter in dogs, to the direct action of acid urine upon the fascia; but this assumption has been contradicted by observations of others.

As for the case here presented, it is certainly more than co-incidental that there

[21] Virchow, R.: Pathologie des tumeurs (translated by Aronsshon). Paris, 1869.

[22] Kossa, J. v.: Zeiglers Beitrage zur path. anat., 29: 160–203, 1901.

[23] Lubarsch, O.: Arbeiten aus dem Path.—Anatomischen Institut in Posen, Wiesbaden 1901.

[24] Wells, H. G.: Chemical Pathology, Philadelphia: W. B. Saunders Co., 1925, 5th ed.

co-existed a number of conditions proven to be most efficient in the experimental production of renal ossification. We refer to the obliteration of renal blood flow of the classical experiment of Sacerdotti and Frattin,[3] spontaneously realized in our own case by the occlusion of the renal artery; and to the ligature of the ureter in Ceccarelli[4] experiment realized in our own case by the defective and incomplete development of the ureter. Although no explanation can be offered on the intimate tissular changes and the metabolic disorders which resulted from the interference both of normal blood flow and urinary output, it is assumed that both factors played an important role in creating the local conditions which made the formation of bone possible.

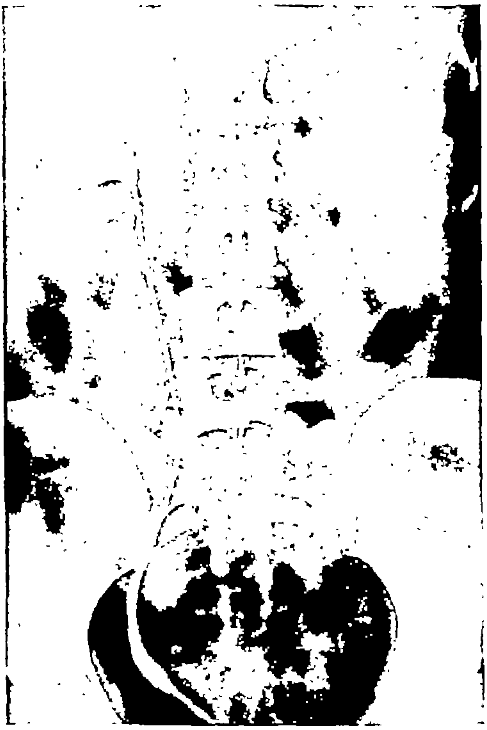

FIG. 4. M. F. Retrograde pyelogram from additional case showing calcified cystic shadows overlying left sacroiliac joint interpreted as calcification in a cystic, ectopic, aplastic kidney.

SUMMARY

The case is presented of an aplastic, nonfunctioning, cystic kidney obtained at operation from a 25 year old white woman. Living bone, provided with bone marrow was found in this defectively developed kidney which apparently resulted from failure of the ureter to join the metanephron during embryonal development. There co-existed a number of conditions proven to be most efficient in the experimental production of metaplastic bone formation in the kidney: obliteration of renal blood flow, realized by the occlusion of the renal artery and impeded urinary output, brought about by the defective and incomplete development of the ureter.

The few similar cases in the literature and the factors underlying renal ossification are reviewed and analyzed.

ADDENDUM

Since our study was submitted for publication, a case probably fitting in the same category of conditions presented by the case above-described has come to the attention of one of us (Dr. Holtham), at the Glover Hospital, Needham, Mass.

A 42 year old white woman complained of persistent pain in the right flank and right lower abdomen. On August 10, 1949 urological investigation showed the absence of the left ureteral orifice and of the ureteric ridge. The urinary findings were not significant. The right kidney and ureter were normal by retrograde pyelogram. There was no left renal shadow in the usual location. Two ring-shaped calcified areas were seen over the left sacroiliac joint and interpreted to be due either to calcification of a cystic left ovary or to a calcified fibroid. The possibility of an aplastic ectopic left kidney with calcification was entertained also.

On March 26, 1952 the urological examination was repeated because of persistent symptoms. Since her previous examination a supracervical hysterectomy was performed; fibromyomas of the uterus and endometrial cysts of the left ovary were found. Exploration confirmed the absence of the left kidney from its normal location. It is unfortunate that the presacral area was not explored by the surgeon. The urological findings were identical with the previous examination and the calcified shadows were still present. A photograph of the radiological findings (fig. 4) is introduced for comparison with those of the foregoing case. Although the exact pathological process is not known, the similarity of clinical and radiological findings indicate the possibility of an identity of situations.

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UNILATERAL POLYCYSTIC KIDNEY IN A NEWBORN

BJORN LIH AND ROBERT E. WAUD

Among the great strides surgery has taken in recent years is the comparative safety with which surgery in the newborn may be carried out. With adequate administration of the proper antibiotics, electrolytes, water and blood, the mortality is steadily lowered and probably should not be much higher than for adults with similar diseases. Since examination of the newborn is more and more being done by qualified physicians, more anomalies are being discovered early and surgery is consequently being carried out at an earlier age with the attending greater chance for recovery.

Our case report of an infant with polycystic kidney illustrates these points. While the majority of patients in which the condition is diagnosed are between the ages of 40 and 60, the disease has been described in fetuses and infants.[1, 2] Again, the majority of these present the disease in both kidneys, although reports of apparently unilateral disease have been published.[2, 3] Whether follow-up over half a century, which probably is necessary, will find these patients with contralateral disease is for the future to decide.

CASE REPORT

D. H., a full term white male infant weighing 3100 gm., was born of a 43 year old mother, gravida 3, para 2, on January 12, 1950 following a normal pregnancy. Postnatal examination by one of us, R. E. W., was apparently negative. Routine nursery procedure was instituted including breast feeding. On January 18 the infant was again examined for discharge, at which time there was observed to be a visible, irregular protrusion of the abdomen. Palpation revealed a large irregular shaped mass in the right flank extending from the costal margin to the right iliac fossa. This was explained to the parents and the infant sent home for one week in an attempt to regain birth weight and to clear up a newborn skin rash.

On January 24 D. H. was re-admitted for diagnostic work-up. At this time it was noted that he had lost 4 ounces and it was thus deemed advisable to discontinue breast feeding and institute an evaporated milk formula.

Physical examination revealed no change from the last examination.

Laboratory findings were as follows:

Urine:	*1-26-50*	*1-29-50*
Specific gravity	Q.N.S.	1.003
Reaction	Acid	Alkaline
Albumin	Ft. trace	0
Sugar	0	0
White blood cells	1-3	rare
Red blood cells	occ.	0
Epithelium	few	occ.

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[1] Rolnick, H. C.: The Practice of Urology. Philadelphia: J. B. Lippincott Co.
[2] Goodyear, W. E. and Beard, D. E.: Am. J. Dis. Children, 76: 203, 1948.
[3] O'Donnell, L. D. and Presti, J. C.: J. Urol., 62: 651, 1949.

Blood:		
Hemoglobin	14.5	13
Red blood cells	4,760,000	3,860,000
White blood cells	13,350 (4 bands)	8,000 (9 stabs)
Polys	38	41
Lymphocytes	34	49
Monocytes	8	8
Eosinophiles	20	2
Basophiles	0	0

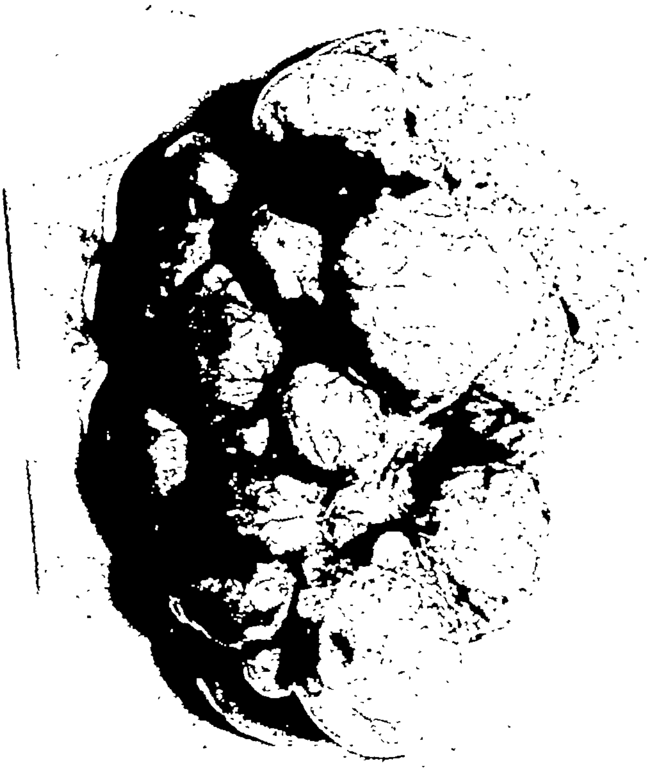

FIG. 1

The CO_2 combining power was 60 vol. per cent. Plasma chlorides, 597 mg. per cent.

On January 24 a subcutaneous pyelogram was reported to show the following: "Examination of the abdomen shows a large, soft tissue-mass filling the right side of the abdomen displacing the intestinal tract downward and to the left. The shadow is continuous with that of the liver. No kidney outlines can be determined.

"Examination after subcutaneous injection of diodrast shows prompt excretion of the material on the left side with a normal kidney pelvis and normal calyces. The kidney pelvis on the right is poorly outlined. It lies downward and toward the midline. There is considerable distortion of the bladder. The appearance is that of a primary kidney tumor on the right side."

Operation was delayed because of diarrhea and temperature which subsided on conservative treatment.

On February 2, when the infant was 18 days old, laparotomy was performed by one of us, B. L. The operative note follows: "The right kidney was completely replaced by a polycystic mass containing cysts measuring up to 4 cm. in diameter. Over all, the mass was 12 by 8 by 8 cm. in size. No normal kidney substance could be identified. The left kidney was carefully palpated and no abnormalities could be noted. The remainder of the abdominal viscera, particularly the liver and pancreas, appeared to be normal to palpation and inspection."

Pathological report: "Gross specimen consists of a kidney measuring approximately 8 by 7 by 6 cm. (fig. 1). The entire specimen seems to be composed of cystic masses varying in size from approximately 1 cm. up to 4 cm. in diameter. All of these appear greyish-white in color and are fibrous and contain clear fluid. The inner surfaces of all, as far as can be determined, are smooth and glistening. On multiple section through this cystic structure, there is no discernible renal tissue found. Representative sections are taken and the remainder of the specimen saved."

"Histology: Sections show chiefly cystic structures in a fibrous-like stroma. There are some cysts lined by cuboidal and columnar epithelium, others lined by pseudo-stratified, transitional-like epithelium. In a few small areas, there are abortive, glomerular structures, sometimes surrounded by varying number of small tubules. There are some focal areas of lymphocytic cell infiltration. Diagnosis: Polycystic kidney."

The patient was discharged on February 10 following a relatively uneventful postoperative course, at which time he was eating well and gaining weight. The patient has received regular checkups since discharge and has continued to do well. At 5 months of age he weighed 7430 gm., a gain of 4330 gm.

SUMMARY

A case of apparently unilateral polycystic disease of the kidney occurring in a newborn is presented. An effort will be made to follow this patient for life. The importance of thorough examination of the newborn and the safety of surgery in infants is stressed.

Richland, Wash.

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CONGENITAL SOLITARY KIDNEY

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Because of the intricate embryologic development of the urogenital apparatus, congenital anomalies occur in the kidney more frequently than in any other organ of the body. These malformations do not, in themselves, constitute a serious threat to life, but some patients who have such anomalies tolerate genitourinary disease poorly. Renal anomalies are therefore, as a rule, important because of the associated complicating conditions, the commonest of which are urinary infection and obstruction, and the formation of calculi. Gutierrez has stated that congenital renal anomalies are responsible for 40 per cent of all pathologic lesions involving the kidneys. This belief stems from the widespread use of excretory urography as a diagnostic aid since 1929. Although developmental errors of form, position and structure are more prone to cause disease than anomalies of number, renal agenesia remains one of the most interesting and diagnostically important of all urologic entities.

Congenital solitary kidney was first described by Aristotle. A review of the world literature to 1932 by Collins disclosed only 581 cases of authenticated congenital solitary kidney. In the majority of these cases, the anomaly was discovered at necropsy. Since the number of clinically recognized and proved instances of this anomaly has increased tremendously, it is now possible to detect accurately the presence of a true single kidney from certain urographic and cystoscopic findings which will be discussed later.

Congenital solitary kidney signifies a complete lack of development of the opposite organ. The single kidney is, therefore, derived from but one renal bud. A real understanding of the genesis of this condition justifies brief reference to certain pertinent embryologic facts. The ureteral bud, which sprouts from the dorsal side of the wolffian duct near the cloaca during the fourth week of fetal life, ordinarily invades the nephrogenic blastema, which gives rise to the formed kidney. Although the renal anlage may develop without the formation of a ureteral bud and vice versa, a complete ureter usually is not found unless renal vestigial tissue is present.

Certainly, defective germ plasm may be loosely attributed to be of etiologic significance. One may accept genetic failure or regression of the ureteral bud as responsible for renal agenesia, but whether the developmental error should be assigned to the pronephros, mesonephros or metanephros is purely conjectural.

Braasch and Merricks reported 69 cases of congenital solitary kidney which were observed at the Mayo Clinic prior to 1937. In 27 of the 69 cases, the diagnosis was verified at operation or necropsy. In 1932, Collins reported 9 cases in which a diagnosis of this anomaly was made in the Section on Pathologic Anatomy of the clinic.

Unilateral renal agenesia is found in about 1 of every 1,000 cases in which necropsy is performed. In clinical practice, it is found in approximately 1 of every 1,500 cases. These figures suggest that surprisingly few persons who have a solitary kidney go through life without the anomaly becoming manifest. In many cases, however, the signs and symptoms which lead to the discovery of the solitary kidney are not related to the urinary system at all. The anomaly does not have a tendency to occur more frequently on either side. If one considers the over-all incidence, the anomaly does not have a tendency to occur more frequently in either sex. In clinical practice, however, it has been found more frequently in females than in males. This apparent difference in the incidence in the two sexes probably is attributable to the fact that a solitary kidney is associated with complications and other anomalies more frequently in cases in which the patients are females. As a result of the complications and associated anomalies, the patients seek medical consultation, which results in the discovery of the solitary kidney. In about two thirds of the cases, the anomaly is discovered when the patients are between 35 and 45 years of age.

Dees reported that pyelography disclosed a congenital anomaly of the upper part of the urinary tract in 135 (9.6 per cent) of 1,410 cases in which this diagnostic procedure was employed. The anomalies that were encountered most frequently were duplication of the renal pelvis or ureter, and renal fusion (including horseshoe kidney), hypoplasia and ectopia. Of greater urologic importance, however, is the fact that from 50 to 80 per cent of all maldeveloped kidneys are complicated by infection, obstruction or calculi. In 23 (33.3 per cent) of the 69 cases reported by Braasch and Merricks, active pyelonephritis either was present when the patients were examined at the clinic, or it had been present previously. An associated anomaly of the kidney was present in 7 (10.1 per cent) of the cases, and usually was characterized by renal ectopia or failure of rotation of the kidney. Hydronephrosis was present in 6 cases (8.6 per cent), and calculi were present in the renal pelvis or ureter in 6 cases (8.6 per cent). Nephritis and renal tuberculosis occur more frequently in patients who have a congenital solitary kidney than they do in normal persons.

It is well established that genital anomalies are associated more frequently with a congenital solitary kidney than they are with any other type of renal malformation. This is particularly true in cases in which the patients are females. According to Fortune, anomalies of the genital tract were present in 128 (69.9 per cent) of 183 cases of congenital solitary kidney in which the patients were females whereas such anomalies were present in only 42 (21.2 per cent) of 198 cases in which the patients were males. The probable explanation for the higher incidence of associated genital anomalies in females is the later embryologic development of the müllerian ducts as compared with that of the wolffian duct in males. In females, the most common genital anomalies associated with a congenital solitary kidney are true unicornuate uterus, unicornuate or bicornuate uterus with a rudimentary horn, and absence or hypoplasia of the vagina or double vagina. In males, the seminal vesicles, prostate gland or epididymis may be rudimentary, atrophic or absent. Associated anomalies of the testis supposedly are rare. In both sexes, the associated genital anomalies almost always are found on the side on which the kidney is absent.

In cases of congenital solitary kidney, the chief signs and symptoms referable to the urinary tract usually are urinary frequency, pyuria, hematuria and pain in the loin, which are the signs and symptoms of the particular complication that is present. In rare cases, a patient may seek medical advice because of a symptomless mass in the flank, which represents the solitary kidney. Smith and Orkin have emphasized the frequency with which gastro-intestinal symptoms are associated with congenital anomalies of the kidney, and they have used the term "renal digestive reflex" to designate these symptoms. In 46 (66.6 per cent) of the 69 cases previously reported from the clinic, physical examination did not disclose any abnormality. The solitary kidney was palpable in 17 (24.6 per cent) of the 69 cases.

TABLE 1. *Urographic findings suggestive of a congenital solitary kidney*

1. Absence of renal outline and contrast medium on one side
2. Enlarged renal shadow on the opposite side
3. Asymmetry of the outlines of the psoas muscles
4. Renal pelvis of moderate size, which does not parallel the degree of parenchymal hypertrophy
5. Ectopy or malrotation of the single kidney in 5 to 10 per cent of cases

TABLE 2. *Characteristic cystoscopic findings in cases of congenital solitary kidney*

1. Absence of ureteral orifice on one side and absence of ureteral excretion of indigo carmine on anomalous side*
2. Absence or deformity of the corresponding half of the interureteral ridge or of the trigone

* Although both ureteral orifices may appear normal in a few cases, one of them will end in a rudimentary or atretic ureter.

The urographic findings which are suggestive of a congenital solitary kidney are listed in table 1. The cystoscopic findings which confirm the diagnosis are isted in table 2.

MATERIAL

This report is based on a study of 94 cases of congenital solitary kidney which were observed at the Mayo Clinic in a period of 12 years, namely, from January 1, 1938, to December 31, 1949, inclusive. In 5 of the 94 cases, the diagnosis of a congenital solitary kidney was confirmed by operation. In this study, special consideration was given to the clinical, urographic and cystoscopic findings which may be of value in the diagnosis of this anomaly.

RESULTS OF STUDY

The distribution of the patients according to sex did not parallel that reported in the literature, for 57 (60.6 per cent) of the 94 patients were males and only 37 (39.3 per cent) were females. The ages of the patients ranged from 6 to 70 years, and the average age was 37 years. The left kidney was absent in 51 cases (54.2 per cent), and the right kidney was absent in 43 cases (45.7 per cent).

The chief signs and symptoms and the associated pathologic conditions which prompted the patients to seek medical advice are listed in table 3. In 11 of the 94 cases, the patients did not have any signs or symptoms which were attributable to the congenital solitary kidney. In 10 of the 12 cases in which the patients sought medical advice because of the presence of an associated genital anomaly, the patients were females; in the two remaining cases, the patients were males. Hematuria was present in 9 cases. The hematuria was of the essential type in 2 of the 9 cases. It was caused by cystitis in 3 cases and by urinary calculi in 3 cases. In the remaining case, the cause of the hematuria was not determined.

At the time of the initial physical examination at the clinic, the solitary kidney was palpable in only 8 cases. The incidence of hypertension was not significantly higher than it would be in a group of persons of comparable age. In 16 of the 94 cases, the values for the blood pressure were higher than 150 mm. of mercury systolic and 90 mm. diastolic, but only 8 of the 16 patients were less than 50 years of age.

TABLE 3. *Chief signs and associated pathologic conditions which caused patients to seek medical advice*

SIGNS AND SYMPTOMS, AND ASSOCIATED PATHOLOGIC CONDITIONS	CASES
Pain (usually situated on the side of the solitary kidney)	23
Associated genital anomaly	12
Dysuria; urinary frequency and burning	10
Hematuria	9
Recurrent pyelonephritis	4
Painless mass in flank	4
Hypertension	5
Disturbances of urinary control	4
Pyuria	2
Albuminuria	3
Miscellaneous conditions	7
Total	83*

* In 11 of the 94 cases, the patients did not have any signs or symptoms attributable to the solitary kidney.

Associated congenital anomalies were present in 37 (39.3 per cent) of the 94 cases. The incidence of these anomalies according to the sex of the patients did not parallel that reported in the literature, for 20 (54.1 per cent) of the 27 patients were females and seventeen (45.9 per cent) were males. The associated anomalies which occurred in the 17 males are listed in table 4, while those which occurred in the 20 females are listed in table 5. Furthermore, the incidence of associated genital anomalies was only slightly higher (43.2 per cent) in females than it was in males (21 per cent). With the exception of bilateral or midline defects, the associated congenital anomaly was situated on the side on which the kidney was absent in all but 2 cases. Contrary to most reports, anomalies of the testis were observed rather frequently.

The most common complication encountered in this series of 94 cases was urolithiasis, which occurred in 12 cases (12.7 per cent). In 10 (10.6 per cent) of the cases, excretory urography disclosed changes which were suggestive of chronic pyelonephritis. Hydronephrosis was present in 8 cases, and glomerulonephritis was present in 4 cases.

Excretory urography was performed in all of the 94 cases. This diagnostic procedure disclosed malrotation of the solitary kidney in 11 cases (11.7 per cent) and a significant degree of ureterectasis in 7 cases (7.4 per cent). The solitary kidney was ectopic in 5 cases, while slight but definite ptosis was present in 4 cases.

TABLE 4. *Associated congenital anomalies in 17 cases in which the patients were males*

ASSOCIATED ANOMALY	CASES
Atrophy of testis	7
Hypospadias	3
Deformity of spinal column	3
Atrophy of 1 lobe of prostate	2
Cryptorchidism	2
Absence of vas deferens	1
Imperforate anus	1
Urethral diverticulum	1
Perineal fistula	1
Total	21*

* More than one associated anomaly was present in some of the 17 cases.

TABLE 5. *Associated congenital anomalies in 20 cases in which the patients were females*

ASSOCIATED ANOMALY	CASES
Absence of vagina	7
Bicornuate uterus with rudimentary horn	7
Absence of uterus	3
Deformity of spinal column	3
Atrophy of fallopian tube and ovary	2
Atrophy of breast	2
Dextrocardia	2
Double vagina	1
Imperforate anus	1
Rectovaginal fistula	1
Total	29*

* More than one associated anomaly was present in some of the 20 cases.

An effort was made to find some other feature which might be of value in the urographic diagnosis of congenital solitary kidney. In 69 of the 94 cases, the urograms were of sufficient clarity to warrant careful scrutiny. In general, examination of these urograms confirmed Braasch's contention regarding the discrepancy in the relative hypertrophy of the renal pelvis and parenchyma. In most of the cases in which the shadows of both psoas muscles were at all demonstrable, the outlines of the muscles were approximately equal in size and delineation. However, in 8 of the 69 cases, the outline of the psoas muscle was obscured on the side on which the kidney was absent, while a sharp configuration of the muscle persisted on the side of the solitary kidney.

Cystoscopy was performed in 75 of the 94 cases. This diagnostic procedure disclosed absence of one ureteral orifice and the corresponding half of the interureteral ridge or trigone in 37 cases (49.3 per cent). In a third of the cases, one ureteral meatus was absent but the interureteral ridge and trigone appeared to be normal. In 13 of the 75 cases in which cystoscopy was performed, both of the ureteral orifices were visible, but an attempt to perform ureteral catheterization or retrograde pyelography disclosed a blind ureteral lumen at or near the ureterovesical juncture on one side. The single ureteral orifice was ectopic in 4 cases. In 15 cases, cystoscopy disclosed evidence of cystitis or urethritis. In 2 cases, this diagnostic procedure disclosed hypertrophy of the vesical neck, which was relieved by transurethral resection. A vesical diverticulum was present in 2 cases, a ureterocele, in 2 cases, a small polypoid tumor of the bladder, in one case, and a urethral diverticulum, in one case. In the case in which cystoscopy disclosed the urethral diverticulum, the patient was a boy, aged 6 years. The polypoid tumor was treated by fulguration.

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RETROPERITONEAL ENCYSTED HEMATOMAS

ROBERT LEAKE AND T. BRENT WAYMAN

Retroperitoneal encysted hematomas occur as sequelae of traumatic and spontaneous retroperitoneal hemorrhages. The fate of a retroperitoneal hemorrhage depends to a great extent on the amount of hemorrhage. Massive hemorrhages are almost uniformly fatal while small hemorrhages tend toward resorption and spontaneous cure. Between these extremes the fate of the resulting hematoma depends on a number of other factors. Blood-borne infection or extension of infection from neighboring organs usually results in abscess formation. Organization of the hematoma leads to the formation of fibrous masses. Degeneration of blood elements and liquefaction of retroperitoneal fat may stimulate the production of surrounding fibrous tissue and lead to encapsulation. Colston and Baker believe that extensive extravasations of blood and urine, too large to resolve, invariably become encysted. Cyst formation occurred in 6 of the 13 cases they presented in a discussion of the late sequelae of renal trauma. In 1933, Polkey and Vynalek collected 178 cases of spontaneous perirenal hematoma from the literature. Six of these cases, 3 per cent, were described as "pararenal blood cysts" and were probably encysted retroperitoneal hematomas.

The etiology of retroperitoneal hemorrhage excluding the traumatic cases covers a wide variety of causes. Polkey and Vynalek found underlying renal diseases such as tumors, infections, hydronephrosis, glomerulonephritis, polycystic disease, and lithiasis in the majority of their cases. Vascular disease including arteriosclerosis, aneurysms, and periarteritis nodosa were next most common. Diseases of the adrenals, blood dyscrasias, infections, and diseases of the retroperitoneal tissues were also found. In 14 per cent of the cases spontaneous hemorrhages had occurred with no demonstrable cause.

Retroperitoneal hemorrhage due to renal trauma is usually characterized by flank pain, spasm, tenderness, hematuria, and a mass which is either palpable or visible on x-ray. The diagnosis is usually made without difficulty. Acute forms of spontaneous perirenal hematoma are characterized by the sudden onset of severe abdominal pain most marked in the flank, signs of internal hemorrhage—pallor, prostration and shock, and the appearance of a retroperitoneal mass. The chronic forms due to slower bleeding or to repeated small hemorrhages are accompanied by milder symptoms. The pain is less severe and often colicky. It may be entirely absent. Shock would not be expected, but anemia may be present. A sensation of weight or fullness may first attract the patient's attention to a mass in his flank. An encapsulated retroperitoneal hematoma resulting from one of the above forms of bleeding may be suspected if the initial signs and symptoms of the hemorrhage have been present and have been correctly evaluated. If these symptoms go unrecognized or are so mild that they cannot be specifically identified, the diagnosis is almost impossible. The patient under the latter conditions presents the problem of an unexplained abdominal mass; Engel has described the investigation of abdominal masses from the urologists's standpoint and has pointed out the almost constant finding of displacement of the ureters, renal pelves, or kidneys in subjects with extrarenal retroperitoneal masses. The differential diagnosis at this point should include adrenal tumors, pancreatic tumors and cysts, retroperitoneal cysts, and the primary retroperitoneal tumors. The final diagnosis must usually be made by exploration and section of the tumor.

CASE REPORTS

Case 1. H. W. L., a 45 white man (No. 124151) was admitted to the V. A. Hospital, Dayton, Ohio, July 18, 1949. Three weeks before admission he had a sudden onset of generalized abdominal pain while prying open a wooden crate. The pain was so severe that hypodermics were necessary for relief and the patient was hospitalized for observation. Cholecystograms, an upper gastro-intestinal series and a barium enema series were reported negative. The abdominal pain gradually subsided but a residual dull pain persisted in the left flank. An excretory urogram was made. The patient was told that he had a "dropped kidney" and he was referred to the Veterans Hospital for treatment.

On admission the patient complained chiefly of epigastric fullness, bloating, and belching. His abdominal pain and flank pain had completely subsided. He had no urinary symptoms. His past history was essentially negative. Physical examination demonstrated mild left upper quadrant and left flank tenderness. There were no palpable masses. His temperature was 98.8F, pulse 96, respiration 20, blood pressure, 110/60, hemoglobin, 10.5 gm., red blood count 3.8 million. White blood count, 13,750. Urinalysis, negative. Blood urea nitrogen, 16. Serology, negative. A plain x-ray film revealed a vague left upper quadrant mass containing several scattered calcifications (fig. 1, *A*). The left diaphragm was elevated (fig. 1, *B*). Retrograde pyelograms demonstrated a downward displacement of the left kidney (fig. 1, *C*). Perirenal air insufflation outlined the lower margin of a large globular mass superior to the left kidney (fig. 1, *D*). An upper gastro-intestinal series showed anterior and medial displacement of the stomach (fig. 1, *E* and *F*). In summary x-ray studies demonstrated a large retroperitoneal mass above the left kidney. There were no clinical signs or symptoms of adrenal insufficiency or hyperactivity. There had been no fluctuations of the patient's blood pressure. A preoperative diagnosis of primary retroperitoneal tumor was made.

An exploratory laparotomy through a thoraco-abdominal incision was done August 25, 1949. The abdominal portion of the incision was made first. A large tense, cystic tumor could be palpated extending up under the diaphragm. The incision was extended around through the eighth interspace and the diaphragm was divided in the direction of the incision. The cyst was easily exposed by this incision and found to be freely movable. It was entirely separate from the tail of the pancreas, the spleen, and the kidney. The cyst seemed to arise from the left adrenal gland which was incorporated into its posterior capsule. No major blood supply was encountered in the excision of the mass. The postoperative course was satisfactory, and he was discharged on his fourteenth postoperative day. He has been well since discharge. Follow-up pyelograms showed the kidney in normal position.

The specimen was a large cystic mass measuring 18 by 14 by 11 cm. The capsule was tense, dark red, and shiny. At the lower pole showing through the mass were scattered remnants of adrenal tissue. Longitudinal sections through the cyst showed its contents to be fluid and clotted blood. Microscopic sections demonstrated a thin fibrous capsule with no lining membrane. There were no evidences of embryologic rests in any of the sections. There was a thin rim of compressed adrenal tissue present. There was a mild lymphocytic infiltration of the adrenal. Pathologic diagnosis was retroperitoneal encysted hematoma. The original cause of bleeding could not be determined. It was postulated that the hemorrhage had come from the adrenal or from its blood supply. The lymphocytic infiltration of the adrenal was not felt to be significant.

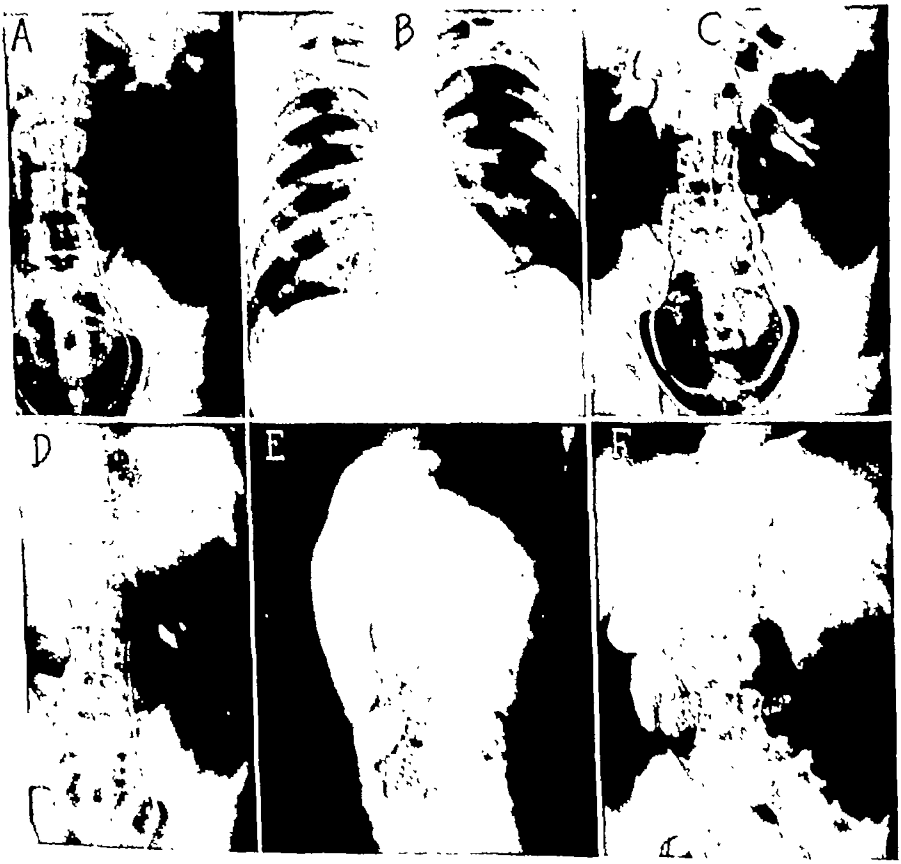

FIG. 1

Case 2 (Dr. Vinton E. Siler's case). M. J., a 42 white housewife (No. 500287) entered the Christian R. Holmes Hospital, Cincinnati, Ohio, March 10, 1950. One week before admission the patient had a sudden onset of nausea and vomiting. Later she developed crampy left abdominal pain which persisted. Anorexia, belching, and bloating were prominent symptoms. Similar episodes had occurred intermittently for a year before admission. A cholecystectomy had been done 19 months before admission without relief. Two days prior to admission she vomited about a cupful of bright red blood. The next day she passed a dark bloody soft-formed stool.

On physical examination the liver was found to be palpable 3 finger breadths below the right costal margin. The liver edge was soft, smooth, and nontender. There was a large palpable pulsating mass to the left of the umbilicus extending up under the left costal margin. There was a thrill palpable over the mass and a bruit could be heard on auscultation. The remainder of the examination was essentially negative. Her temperature was 98.8F, pulse 92, respirations 22, blood pressure 110/70. Urinalysis, negative. Red blood count, 3.35 million. White blood count, 14,850. Hemoglobin, 9.5 minutes. Thymol turbidity, 4.2 u. Serum bilirubin, 0.05 mg. prompt and 1.0 mg. total. Cephalin flocculation, 1 plus in 48 hours. Bromsulphalein test, 4 per cent dye retained in 45 minutes. Chest x-ray, upper gastro-intestinal series, and barium enema were all negative although lateral films were not made. A flat film of the abdomen demonstrated multiple small calcific deposits in the upper abdomen at the level of L2 (fig. 2, *A*). On a lateral film they could be seen anterior to the region of the pancreas. An excretory urogram revealed a mass above the left kidney with distortion and flattening of the superior major calyx (fig. 2, *B*).

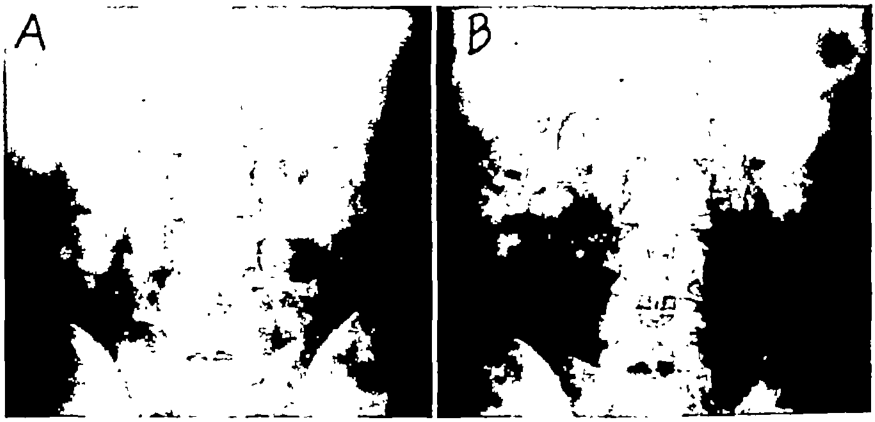

FIG. 2

A preoperative diagnosis of retroperitoneal tumor was made. It was believed that the tumor was either arising from or invading the superior pole of the left kidney. The patient was explored through a thoraco-abdominal incision because of the size and position of the mass. At operation it was apparent that the mass could not have been dealt with through a conventional lumbar or abdominal incision. The mass was found to involve the superior pole of the kidney, the tail of the pancreas, and the spleen. A portion of it was adherent to the diaphragm. The kidney, spleen, and the tail of the pancreas were excised with the mass. Pathologic sections demonstrated a cystic mass 14 by 11 cm. in diameter. The wall of the cyst was formed of dense fibrous tissue which blended with the superior pole of the kidney. There was no lining membrane to the cyst. It was filled with hemorrhagic and necrotic debris. The spleen showed several fibrotic and inactive tubercules. A biopsy of the liver was normal. The pathologists' impression was organizing encysted perirenal hematoma, possibly resulting from a "burned-out" renal carbuncle.

DISCUSSION

Two cases of retroperitoneal encysted hematoma have been presented. The first case had a sudden onset of severe abdominal pain which gradually subsided over a period of several days. This probably represented a single episode of hemorrhage. His late symptoms of epigastric fullness, bloating, and belching must have been due to the pressure of the hematoma on the stomach. The course in this case is not complicated by any extraneous symptoms. The findings seem to indicate that the single hemorrhage took place and was followed by encapsulation of the hematoma in the relatively brief period of 8 weeks. No definite cause of bleeding could be determined in this case. The second patient's history includes repeated episodes of abdominal pain, nausea, belching, etc. Apparently she had had intermittent hemorrhages for a year. The bleeding probably came from the upper pole of the kidney and was probably due to pre-existing renal disease. Both cases were mistaken for primary retroperitoneal tumors. The final pathologic diagnoses were completely unexpected.

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PALINDROMIC UNILATERAL RENAL PURPURA: AN EXPLANATION FOR RENAL HEMATURIA OF OBSCURE ORIGIN

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Hematuria is one of the commonest symptoms of serious urinary tract disease, and is very perplexing when its source and cause are not readily apparent. Urologists are confronted with many such cases. We have performed nephrectomy on 6 patients in whom the cause of bleeding remained obscure even after inspection of the kidney. Following review of the pathological material in these cases it became apparent that certain findings were common to all of them. The histological findings in these kidneys suggested the possibility of an allergic basis for this condition, which is undoubtedly the same entity as many of the cases reported in the literature as "chronic hemorrhagic papillitis." It also became apparent that this is a disease of the entire kidney and not one confined to the papillae. Dr. E. M. Butt, the pathologist, suggested that this condition be called palindromic unilateral renal purpura, better to suggest its principal characteristics.

We will report 6 cases and review the pathology and possible etiology of this condition which may cause prolonged, severe hematuria sufficient to endanger life and require nephrectomy. The study of the pathology of the condition is being continued and will be reported elsewhere in greater detail.

CASE REPORTS

Case 1. (St. Luke Hospital, Number F 486) M. M., a 35 year old nun, had had recurrent gross hematuria for 5 years prior to nephrectomy in 1943. She had been studied cystoscopically many times and was always found to be bleeding from the left kidney. Her bleeding was so severe that many transfusions had been necessary during this period of time. All ordinary forms of treatment including repeated pelvic lavage with silver nitrate had been tried and had been only temporarily beneficial. This patient had an associated extreme degree of nervous and emotional instability resulting in severe muscle spasms and intention tremor which incapacitated her and kept her bedfast. Her urine was negative except for the presence of 3 plus albumin and gross blood. No infection ever was demonstrated. Between episodes of bleeding it was entirely normal. The blood count disclosed a severe secondary anemia and a white blood cell count of 7,250 with 67 per cent neutrophils, 27 per cent lymphocytes, 1 per cent basophils, 3 per cent monocytes, and 2 per cent eosinophils. Other blood studies directed at determining the cause for bleeding had always failed to disclose any cause. Numerous pyelograms during the 5-year period of observation failed to show any abnormalities or changes. In March 1943, the left kidney was removed although the external appearance was normal.

The patient moved to another community a few months later and has not been

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 27, 1951.

examined since. However, she reports by correspondence that she thinks the urine has contained blood on two occasions since the nephrectomy. Her catheterized urine is reported as being normal now, except for 8 to 10 red blood cells per high power field and nonhemolytic streptococci and E. coli. Because of her nervous trouble she sometimes has to be catheterized and this probably accounts for her present infection and two attacks of hematuria. The pathology report on the kidney removed follows: "The specimen is a kidney which appears normal externally and on cut section except for irregular patches of submucosal hemorrhage."

The histology of all cases will follow the last case report.

Case 2. (Los Angeles County General Hospital P.F. 130-512.) V. H., a 45 year old housewife, entered the hospital in December 1938, complaining of hematuria of 2 to 3 weeks' duration. In 1929 she was given a course of treatment for syphilis. Cystoscopy several times during this admission revealed a bloody jet from the left ureteral orifice. The renal function bilaterally was normal and the pyelograms were within normal limits. The urine on admission showed an occasional pus cell and on some occasions a few gram negative bacilli were noted. No tubercle bacilli were found. The red blood cell count was 4,760,000 and the hemoglobin 14 gm. The white blood count was 10,600. No differential count was done. The platelet count was 251,000. The bleeding time was 4 minutes and the clotting time 9 minutes. The blood calcium was 9 mg. The blood pressure was 110/70.

The patient continued to bleed intermittently until 1943 and repeated cystoscopic examinations disclosed it always to be from the left kidney. The pyelograms were repeatedly interpreted as being normal. Pelvic lavage on several occasions with 1 to 3 per cent silver nitrate solution failed to make any change. Treatment with sulfonamides and vitamins failed to cause improvement.

On October 18, 1943, a left nephro-ureterectomy was performed. No gross abnormalities were noted.

The patient has been followed since 1943 and has had no recurrent hematuria. The urine has remained normal. A cystoscopic examination September 8, 1949 failed to reveal evidence of disease. The only differential blood count ever performed on this patient was done in 1946 and disclosed no eosinophils.

The pathology report was as follows: "The specimen is a kidney measuring 10.4 by 4.8 by 3.2 cm. with ureter attached. The capsule strips with relative ease. The cortex and medulla appear grossly normal. The cortex measures 5 to 7 mm. in thickness. One 5 mm. cyst is present in the cortex. Irregular areas of submucosal hemorrhage are present in the pelvis."

Case 3. (St. Luke Hospital, Number L 3439.) Mrs. B. T., the 42 year old wife of a physician, was first seen in July 1948, complaining of sudden onset of left flank pain, followed by gross hematuria. She was tender in the left costovertebral angle and across the entire lower abdomen. There was induration by pelvic examination in the left adnexal region. The blood pressure was 122 mm. of mercury systolic and 84 diastolic. A cystoscopic examination revealed a left ureteral orifice which was swollen and hemorrhagic and from which there was a bloody jet. A pyeloureterogram disclosed slight left caliectasis and pyelectasis with marked irregularity of the lower ureter (fig. 1). It was thought that a calculus might have been passed recently from the left kidney. The blood count was as follows: Red blood count 3,920,000; hemoglobin 12.2 gm.; white blood count 5,650; neutrophils 56 per cent; eosinophils 3 per cent; lymphocytes 30 per cent; and monocytes 11 per cent. The urine was as follows: pH 6.0, specific gravity 1.003, albumin 1 plus, sugar none, acetone none, and bile none. The microscopic examination showed 3 to 4 leukocytes per high power field and a few squamous epithelial cells. There was a positive benzidine test for blood. No organisms were found on Gram's stain. The Wassermann and Kahn tests were negative. The highest temperature was 99.6F.

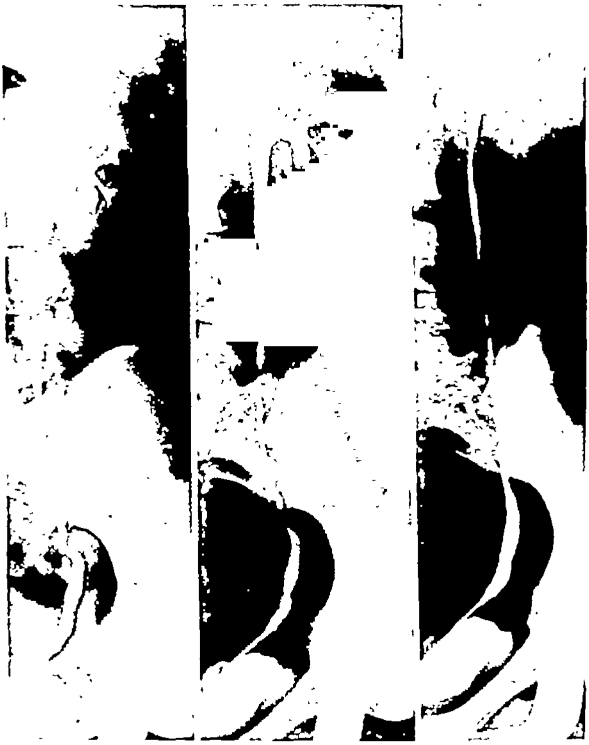

FIG. 1. Case 3. Left pyelo-ureterograms showing irregularity of ureter, particularly in lower third. This was only case with ureteral involvement and only one with pyelographic changes attributible to disease.

The patient remained well until June 1949, when left flank pain and hematuria recurred. The physical, cystoscopic, and x-ray findings were the same as at the time of the first attack. The blood count was as follows: Red blood cells, 4,330,000; hemoglobin 14.3 gm.; white blood cells 5,000; neutrophils 65 per cent; eosinophils 4 per cent, lymphocytes 27 per cent; monocytes 4 per cent. The urine showed albumin 2 plus and was grossly bloody. No bacteria could be demonstrated in the urine.

A left nephro-ureterectomy was performed June 30, 1949. The lower ureter was first explored. It was found to be thick, indurated, hemorrhagic and edematous in the lower third. The nature of this process was uncertain and left no alternative to the operation performed. The subsequent course has been uneventful and the patient remains well. The pathology report was as follows: "The specimen consists of a slightly enlarged kidney which measures 13 by 6.5 cm. After stripping the capsule the surface of the kidney is very pale with occasional petechial hemorrhages present. Some of these are grouped to produce purplish patches on the surface. The cut surface shows a pale cortex about 1 cm. in thickness with pale pyramids. The mucous membrane in the pelvis may be slightly thickened. The ureter measures 27 cm. in length, is dilated and measures 20 mm. in circumference in the widest place. In the upper third of the ureter there are a number of small hemorrhages, but in the distal portion the mucosa is hemorrhagic throughout, and the wall appears to be somewhat thickened. It is difficult to say whether there is any ulceration or not, but apparently there is, since there are some stringy pieces of mucosa measuring about 4 cm. in length. In the thickest part the ureter measures 5 mm. in thickness (fig. 2).

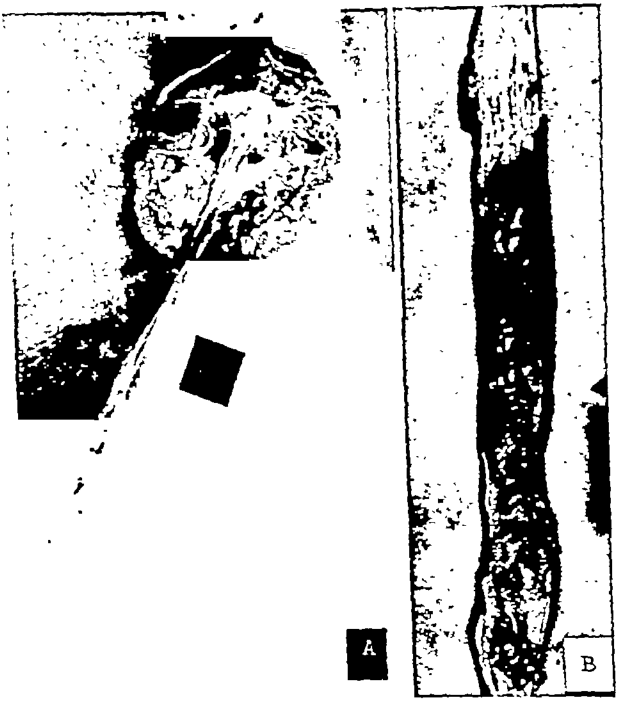

FIG. 2. Case 3. A, kidney and ureter. Hemorrhagic necrosis in ureter and submucosal pelvic hemorrhages and cortical hemorrhage are noteworthy. *B*, close-up of ureter in same case, showing most involved area.

Case 4. (St. Luke Hospital, Number M-1963). Mrs. G. M., a 49 year old office worker, was first seen in January 1950, because of right flank pain of 4 days duration and gross hematuria of 3 days duration. No unusual physical findings were noted. The blood pressure was 128 mm. of mercury systolic and 76 diastolic. Cystoscopic examination disclosed a bloody efflux from the right ureteral meatus. Retrograde pyelograms disclosed a normal left kidney and a moderately dilated right renal pelvis with incomplete filling of the upper calyx. A specimen was collected from the right kidney for Papanicolaou stain. Cells were found in the sediment which were thought to be malignant. The red blood count was as follows: 4,080,000; hemoglobin 11.6 gm.; white blood count 4,600; neutrophils 65 per cent; eosinophils 4 per cent; basophils 1 per cent, lymphocytes 24 per cent; monocytes 6 per cent. The platelets were normal and the smear appeared to be normal. The serology was negative. The urinalysis was as follows: pH 4.5; specific gravity 1.015; albumin 3 plus; sugar none; acetone none; microscopic 4 plus red blood cells, occasional epithelial cells and white blood cells. The Gram's stain disclosed no bacteria and the culture showed no growth. A guinea pig injected with urine subsequently disclosed no tuberculosis at autopsy. A blood transfusion was administered on January 22, 1950 and a mild urticaria resulted. This was treated with oral benadryl. Hematuria continued and a right nephrectomy was performed on January 27, 1950. The course was uneventful and the patient was discharged on the tenth postoperative day.

She was readmitted 2 weeks after discharge complaining of weakness, nightsweats, and headache, beginning 1 week after going home. There was tenderness and a questionable small mass deep in the anterior part of the wound. A chest x-ray was normal and a plain x-ray of the abdomen disclosed nothing unusual. The temperature ran as high as 100F, and this continued for 5 days. The red blood count was 4,040,000 and the hemoglobin was 11.8 gm. The white blood count varied between 8,100 and 9,300 with 64 to 79 per cent neutrophils, of which no more than 9 per cent were stabs. The eosinophils were once 1 per cent and once 4 per cent. The platelet count was 130,000. The sedimentation rate on readmission was 103 mm. in 1 hour and went up to 110 four days later and down to 94 mm. 10 days later. The clot retraction time was normal. There was no increased fragility of red blood cells. The Lee and White coagulation time was 10 minutes (two tubes). The urine was normal repeatedly except for a faint trace of albumin on two occasions. Repeated blood cultures were sterile. Curiously, and without apparent explanation or other findings or anticoagulant therapy, the prothrombin time on February 31, 1950 was 18 per cent. This rose as follows: February 23, 49 per cent; February 25, 68 per cent; February 28, 80 per cent; March 1, 85 per cent.

The patient was treated with pyribenzamine and chloromycetin and in the course of a week became symptom free and was discharged 10 days after admission. The urine, blood count, prothrombin time and sedimentation rate remained normal 6 months later.

The pathology report on the right kidney follows: "The specimen consists of a kidney measuring 11 by 6 by 5 cm. There is a small amount of hemorrhage just below the true capsule which extends a short distance into the kidney substance. The pelvis is very slightly dilated and the mucosa is roughened, thickened, and covered with irregular areas of hemorrhage. The mucosa of the ureter appears to be within normal limits (fig. 3)."

Case 5. (Los Angeles County General Hospital P.F. 737-965.) A. B., a 42 year old Caucasian laborer, first entered the hospital January 5, 1941, because of hematuria of 5 weeks duration. The urine was grossly bloody and was not otherwise unusual. It contained no bacteria and a guinea pig injected with urine disclosed no tuberculosis. The nonprotein nitrogen was 25 mg. per cent. The red blood count was 4,500,000; the white blood count 7,600 with 65 per cent neutrophils. The blood pressure was 120/54. Cystoscopic examination on several occasions disclosed the bleeding always to be from the right kidney. Pyelographically the right kidney did not appear unusual. There was partial renal duplication on the left side. Right nephrectomy was finally performed on March 25, 1941 after repeated episodes of hemorrhage from this kidney. The patient remained well when last seen one month after operation.

The description of the kidney was as follows: "The specimen consists of a kidney weighing 153 gm. and measuring 12.5 by 5.5 by 4 cm. The external surface is pale grayish-brown and smooth. The casule strips with relative ease and is of normal thickness. The kidney shows a normal relationship between the cortex and medulla. The cortex measures from 0.7 to 1.2 cm. in thickness. The cut section reveals a surface which is quite greasy and there is apparently some fat in the kidney substance. The pelvis is moderately dilated and there are numerous submucosal hemorrhages. There is some thickening of the pelvis and the calyces reveal moderate dilation and likewise expose submucosal hemorrhages. The ureter is of normal size and there are some yellowish nodules on the mucosa at the cortico-pelvic junction. These nodules measure from 1 to 3 mm. in diameter."

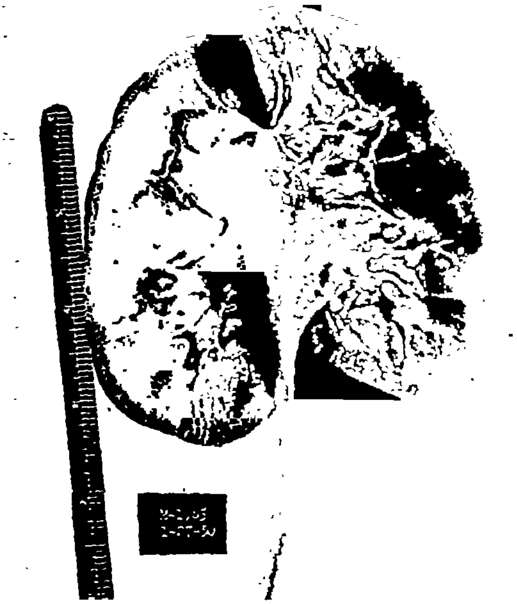

FIG. 3. Case 4. Kidney removed. Dark areas in pelvis are due to submucosal hemorrhage.

Case 6. (Los Angeles County General Hospital P.F. 837-772.) M. F., a 27 year old Caucasian housewife, *first noted gross hematuria and entered the hospital* in April 1949, three days after the onset, following attempted self-abortion. She had a previous entry in 1943 for pre-eclamptic toxemia, when her urine disclosed 4 plus albumin and 2 to 3 granular casts per high power field, but no red blood cells. Following this delivery she re-entered the hospital for a normal delivery in 1947 at which time her urine disclosed 2 to 3 red blood cells per high power field.

At the time of her first episode of bleeding in 1949 the source was found to be the right kidney and the pyelograms were not diagnostic of disease. The urine was normal otherwise, including culture, guinea pig inoculation and Papanicolaou stain. Hemoglobin was 10 gm. and the white blood count was 8,850. A differential count was not done. The clotting time was 6 minutes. The blood serology was negative. The blood pressure was systolic 114 and diastolic 70 mm. of mercury.

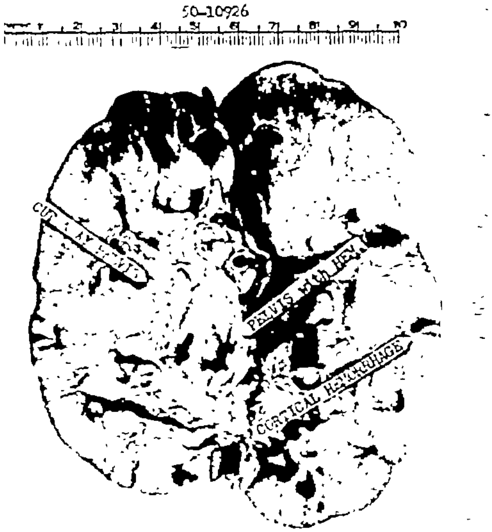

FIG. 4. Case 6. Kidney removed. Areas of hemorrhage are labeled.

There were four subsequent admissions for gross hematuria, culminating in right nephrectomy in September 1950. Each time the bleeding was from the right kidney and pyelograms were not abnormal. Several blood transfusions were necessary. Repeated guinea pig inoculations failed to disclose tuberculosis. On one occasion Aerobacter aerogenes was cultured from the urine.

The description of the kidney was as follows: "The specimen is a kidney with faint fetal lobulations with 6 cm. of ureter attached. It measures 12 by 6.5 by 3.5 cm. Multiple hemorrhagic areas are noted, particularly over the upper pole. Petechiae are present in the lining of the pelvis and there are hemorrhagic streaks radiating through the medulla and cortex" (fig. 4).

HISTOLOGY

Since the histological findings of the 6 cases were similar except for quantitative variations, a single description is presented. All kidneys contained small interstitial scars infiltrated with lymphocytes, in some instances associated with eosinophils. Moderate numbers of the tubules of each kidney contained red blood cells. These hemorrhages were more frequent in the narrow ascending portions of Henle's loops and ducts of Bellini.

A most interesting finding was the presence of hemosiderin in small amounts in the tubular epithelium of all cases. The vascular changes in the cortex were negligible and in no instances were the findings of periarteritis noted. The microscopical changes in the pelves were more pronounced. Epithelial hyperplasia or mucosal thickenings were noted in minor calyces and pelves. Numerous small areas of hemorrhage were found in the subepithelial tissues, in some instances elevating the mucosa. The supporting fibrous tissue was edematous and diffusely but moderately infiltrated by lymphocytes and eosinophils. Cases 1, 4, 5 and 6 had rather large numbers of eosinophils. In the remaining 2 cases eosinophils were difficult to find. The capillaries and small veins were dilated and in some instances scar tissue was noted in relation to the dilated veins. However, as in the cortex, the arterioles and small arteries were without change. The alterations in the ureter of case 3 were similar to the pelvic lesions.

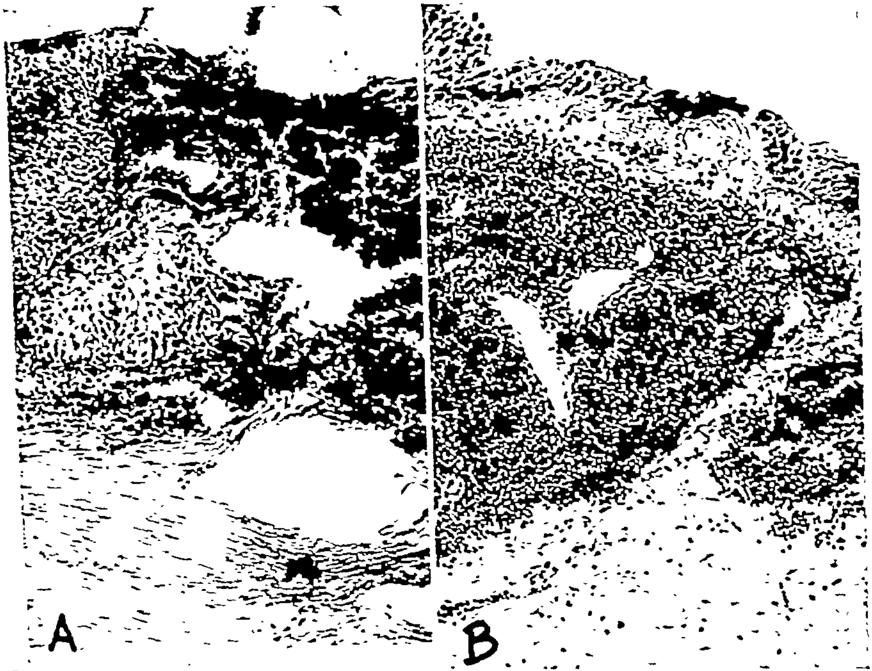

FIG. 5. *A*, photomicrograph × 100 of renal pelvis in case 3 showing thickening of mucosa and hemorrhage elevating pelvic mucosa. *B*, photomicrograph × 100 of pelvic mucosa in case 4 showing detachment of pelvic mucosa due to large hemorrhages. Note fibrinous deposition below epithelium.

The histological lesions were in all instances quite tenuous, difficult to evaluate and without significance, combined or separately, in suggesting a relationship to known pathological entities. However, it must be apparent that the changes are of the total kidney and its contiguous structures, with the major findings in the pelvis. In no instances were hemangiomas found. Furthermore, a papillitis was not evident.

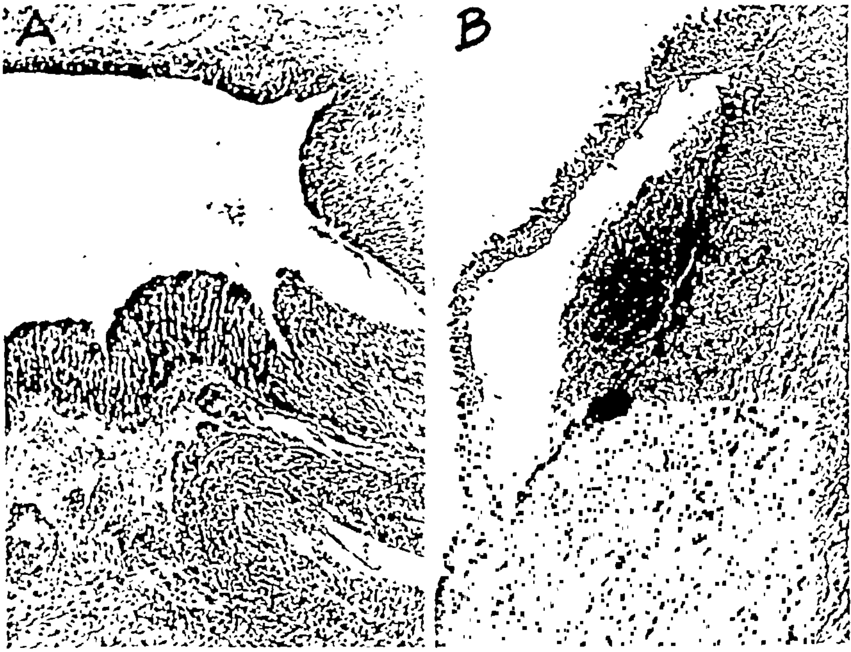

Fig. 6. *A*, photomicrograph of renal pelvis × 75 in case 3. Note thickening of pelvic mucosa, edema of subepithelial tissues with infiltration of eosinophils and lymphocytes; dilation of capillary spaces and small hemorrhages. *B*, photomicrograph of renal pelvis × 75 in case 6 showing hemorrhage in subepithelial tissues with elevation of mucosa. Edema and moderate infiltration of lymphocytes and eosinophils in wall of pelvis are also seen.

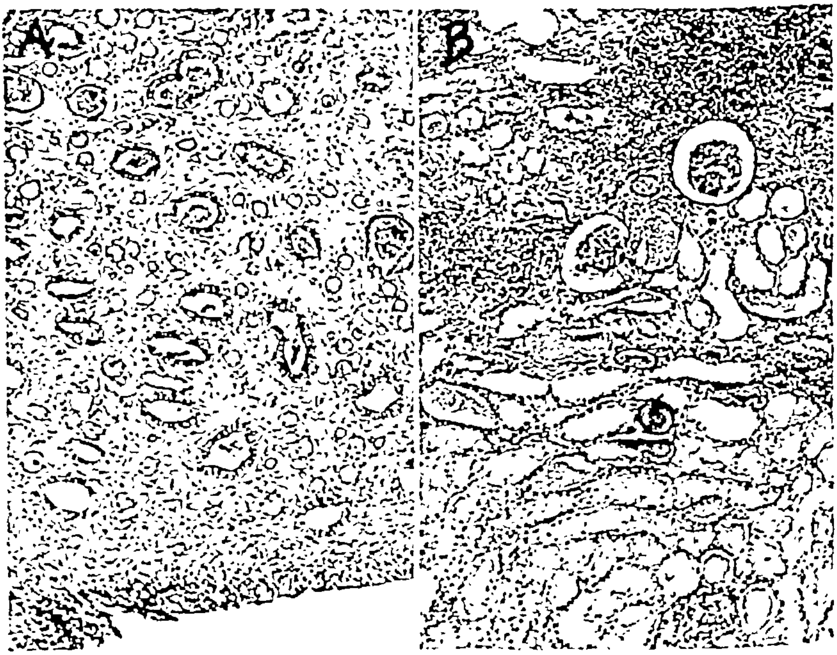

Fig. 7. Case 6. *A*, photomicrograph × 75 of kidney showing hemorrhages in ducts of Bellini. *B*, interstitial scarring with lymphocytic and eosinophilic infiltration and hemorrhage in tubules.

Additional studies are being made, since the histological pattern described was based on the study of a few sections from each kidney (figs. 5, 6, 7 and 8).

LITERATURE

The literature of so-called essential hematuria deals principally with instances of renal varix and angioma. McKay, Baird, and Lynch in 1949 discovered 18 cases in the literature diagnosed as renal varix and 54 cases diagnosed as angioma of the kidney. They reported in addition, 1 case of vascular irregularity of their own.

In contrast, they noted specific mention of no more than fifteen instances of gross hematuria in which examination of the kidney was said to disclose hemorrhagic and inflammatory changes in the papillae. Three of these cases in the literature were described in sufficient detail to be reasonably certain that they were similar to one of the cases which they were reporting. Two of the three similar cases were reported in 1920 by Quinby and showed distinct evidence of inflammatory reaction and evidence of vascular injury. The third was reported in 1924 by MacGowan. The pathological diagnosis in the latter was "chronic hemorrhagic papillitis."

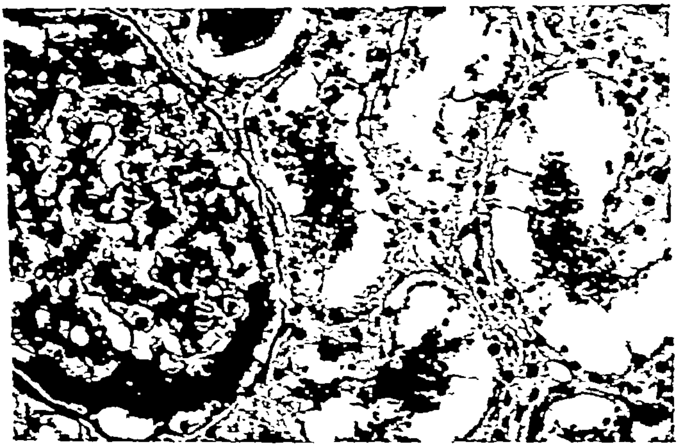

FIG. 8. Case 6. Photomicrograph × 320 of kidney showing hemorrhage in glomerular space and proximal convoluted tubules.

That other instances of this condition have long been noted is apparent from the fact that reference has often been made to such a pathological process, beginning with Braasch's mention in 1914 of the fact that he had seen several cases in which nephrectomy had been done for intractable hematuria and the kidneys found to show chronic papillitis, some with and some without pus and colon bacilli in the urine.

One of the striking features of the histological picture in our cases was the presence of numerous eosinophils. Of the cases noted in the literature only in the case of MacGowan diagnosed as chronic hemorrhagic papillitis and the second case of McKay, Baird, and Lynch are eosinophils similarly described.

DISCUSSION

Priestley and Wilbur, in discussing 100 cases of essential hematuria from the Mayo Clinic, from which ten surgical specimens were available for histological examination, reported that changes were found in all cases in the tips of the papillae, beneath the pelvic epithelium covering the papillae or in the angle formed by the papillae and the pelvis, or in the submucosa of the nearby pelvic tissue. The changes were variable in degree, extent, and type, but were grouped as vascular or hemorrhagic; acute, or chronic inflammatory changes; and fibrotic changes. In almost all, dilated venules and capillaries were present beneath the epithelium at or near the tip of one or more papillae.

This is a succinct summary of the recognized pathological change of so-called essential hematuria. We believe, however, that some of the histological aspects of the lesion found in our cases are more common, and hence more important, than has been realized. These include the presence of eosinophil infiltration previously mentioned, particularly in the pelvic submucosa, as well as bleeding into glomerular spaces and tubules, pigmentation of tubular epithelium, submucosal edema and lymphocyte infiltration, and cortical scarring, with eosinophil infiltration of the scars in one case.

It is possible that the vascular lesions, the inflammatory lesions, and the fibrotic changes described by Priestley and Wilbur are all part of the same pathological process. Perhaps the cellular infiltration so prominent in our cases was less pronounced or overlooked in many of the cases reported as resulting from vascular distention and disruption within the papillae.

Quinby, in 1920, reported 2 cases of so-called essential hematuria, one of which primarily disclosed vascular changes and the other inflammatory reaction. Dr. E. W. Goodpasture was the pathologist who examined these specimens. The first was characterized primarily by vascular distention, rupture and hemorrhage especially prominent in the tips of the pyramids. Dr. Goodpasture postulated that this might be due to mechanical rupture of blood vessels by distention or injury of thin walled vessels by circulating injurious agents.

In the second case there was, in addition to hemorrhage, definite evidence of inflammatory reaction accompanying the vascular injury. No bacteria could be found in the tissue, however. The type of inflammatory reaction indicated to Dr. Goodpasture the presence of a local injurious agent in this case, although its nature was not apparent.

In the case reported by Dr. MacGowan there was described marked round cell and eosinophil infiltration, in addition to new-formed connective tissue with replacement of tubules and a partially organized hemorrhagic area.

Dr. Paul Kimmelstiel, the pathologist who examined the kidney, removed by McKay, Baird, and Lynch, described the microscopic sections as follows: "Histologic sections through various portions of the kidney, particularly those including the grossly hemorrhagic papillae, show an extensive inflammatory infiltration in the medullary and peripelvic portion consisting of lymphocytes, eosinophils, and in some places numerous polymorphonuclear leukocytes. Also there is found granulation tissue which is moderately rich in capillaries. Other foci of inflammatory infiltration with small round cells are found at the corticomedullary junction and even in the cortex connected with occasional foci of scarring in the cortex. The inflammatory infiltration is found to be rather extensive around the peripelvic veins and in one area the histologic findings are suggestive of a direct continuity between a moderate sized vein and a markedly inflamed portion of the calyx. In this area is also found extensive necrosis of the peripelvic tissue with massive hemorrhage. In the immediate vicinity of one of these areas are found occasional multinucleated giant cells, apparently buddings of incompletely developed capillaries. Interpretation: Focal, partially necrotizing pyelonephritis in isolated calyces with massive hemorrhage."

McKay, Baird, and Lynch postulate that these lesions may be due to some organism which it was not possible to demonstrate because of ignorance of its nature.

The lesions described in these kidneys leave little doubt that they were of the same nature as those noted in the cases which we have reported.

If the cause, diagnostic criteria, and a course of treatment for this condition could be evolved it might be possible to clarify the diagnosis in many cases of obscure hematuria and to obviate nephrectomy in many of those not due to neoplasm.

The hemorrhage in these cases characterized histologically by a predominance of dilated venules and capillaries has been said (Bobbitt, et al.) to be due to congenital weakness of the thin walled vessels. Randall, Spitzer and others have explained the dilation and hemorrhage on the basis of renal congestion. Payne and MacNider suggest that this congestion results from corticomedullary scarring resulting from previous infection.

Van der Zwaag demonstrated by elastin staining of a kidney removed from a patient with essential hematuria that the elastin material of several small veins had crumbled, whereupon a rent in the vascular wall had occurred. Mingazzini, expanding the theories of Allemann, Fuchs and Hunner, believes that these vascular rents result from spasm of the urinary passages, either primary or secondary to localized infection, with resultant distention and rupture of the fragile veins.

Borsotti explained a case of essential hematuria observed by him as resulting from a vasomotor disturbance involving the capillaries, particularly of the glomerular rete, resulting in spasm. This he believed to be caused by changes in the tissue metabolism resulting from alterations in the hormonal content of the blood.

While the mechanism of hemorrhage from some of these kidneys may be partially explained by the foregoing postulates, the etiological explanation is inadequate unless it may indeed be some undiscovered infection.

The term "palindromic unilateral renal purpura" was suggested by Dr. E. M. Butt for the condition which we have described. The palindromic, or recurrent nature of the condition is apparent from the clinical histories. The purpuric nature of the lesion is denoted by hemorrhage due to vascular changes characterized by reversible alterations of as yet unknown character in the walls of the smaller vascular radicles which make possible the escape of whole blood from the vascular bed. The hypothesis that this condition is of an allergic nature is based on the histology, the clinical course and the lack of a better etiological concept. Sir William Osler, in 1914, stated that "perhaps the anaphylactic key will unlock the mysteries of the purpuras." (Madison). It certainly seems to be the most likely explanation for the purpura described here.

The eosinophil has been shown to play an active part in allergy, and, indeed, to be the probable vehicle for the histamine which produces the allergic response (Dalton). The eosinophil infiltration was a prominent part of the picture in our cases.

Another interesting finding in some of our cases was the presence of hemorrhage into the tubules and glomerular spaces. The cause and significance of these findings are not clear. In the past it has led to a diagnosis of glomerulonephritis in some cases. The uniform presence of tubular pigmentation was another interesting finding.

The pathogenesis of the condition which we have described is intriguing but obscure. The prolonged course and unilateral extent of the lesion can not be explained. The production by Cavelti and Cavelti of classical glomerulonephritis in animals by the injection of a mixture of killed streptococci and ground kidney extract of the same species, a definite allergic reaction, suggests a possible etiological explanation. The fact that one kidney could be spared this glomerulonephritis by clamping the artery foı 10 minutes after the injection was made may also be of some significance with respect to the unilateral nature of renal purpura.

The diagnosis of palindromic unilateral renal purpura is so far a matter of histopathology. However, it may be suspected in any case of recurrent unilateral hematuria without other demonstrable medical or urological cause for bleeding.

Treatment consisting of blood transfusions, sulfonamides and antibiotics, vitamin K and brief courses of antihistamine drugs has not been curative in individual cases. Antihistamine drugs in larger dosage and over longer periods of time might be helpful. Adrenocorticotropic hormone, which has been demonstrated to be beneficial in some allergic diseases (Bordley, et al.) would be worth trying. Moccasin venom has been reported to be beneficial in essential hematuria (Watkins and Thompson). Silver nitrate irrigations to the renal pelvis have been beneficial only temporarily. Also vitamin C has been reported to be temporarily beneficial (Burkland). In some of our cases nephrectomy was a life-saving procedure.

While a logical explanation of the pathogenesis and treatment of renal purpura thus must await further experimental investigation and clinical observation, it is our belief that it is a definite clinical entity and merits such study.

SUMMARY

The background and literature of essential hematuria and chronic hemorrhagic papillitis are reviewed.

Six cases of prolonged, recurrent, unilateral hematuria without apparent cause, pyelographic change or gross external renal disease are reported.

These cases showed a common histological picture consisting essentially of submucosal hemorrhage and lymphocyte and eosinophil infiltration, bleeding into glomerular spaces and tubules, pigmentation of the tubular epithelium and cortical scarring.

Because of the clinical course, the histological picture, and other evidence reviewed, the term palindromic unilateral renal purpura is suggested for this disease.

It is our belief that the condition described is identical with the majority of the cases hitherto referred to as "chronic hemorrhagic papillitis," as well as those of true "essential hematuria."

The cause and pathogenesis of this condition are unknown. However, the evidence is reviewed which leads us to believe that it may be on an allergic basis.

No curative treatment except nephrectomy has been discovered.

ADDENDUM

In the *British Journal of Urology* (September 1951, p. 233), K. Whittle Martin presents a comprehensive paper entitled "Purpura of the Urogenital Tract." He details 2 cases in which the diagnosis was primary renal purpura, and which seem to be identical with the cases presented here. Martin also hypothecates a hypersensitivity basis for this condition.

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THE ROLE OF INFECTION IN NEPHROLITHIASIS

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The role of infection in nephrolithiasis may be discussed under the following topics: 1) the role of bacteria in the formation of an original stone, 2) the role of bacteria in recurrence of stone, 3) the effect of bacteria as a secondary invader due to the presence of stone and 4) the suggested treatment of the infection when present.

THE ROLE OF INFECTION IN STONE FORMATION

This phase of the subject will be mentioned only briefly. Many investigators hold to the opinion that bacteria play an important part in original stone formation. Others believe that it plays a very minor part, if any at all. Those who hold to the former view conceive the mechanism to be a) the initiation of the Randall plaque by the production of damaged or necrotic tissue at the renal papilla by bacteria, b) the bacteria forming the nucleus of the stone formation and c) the disturbance of the colloid and crystalloid balance in the hypertonic urine.

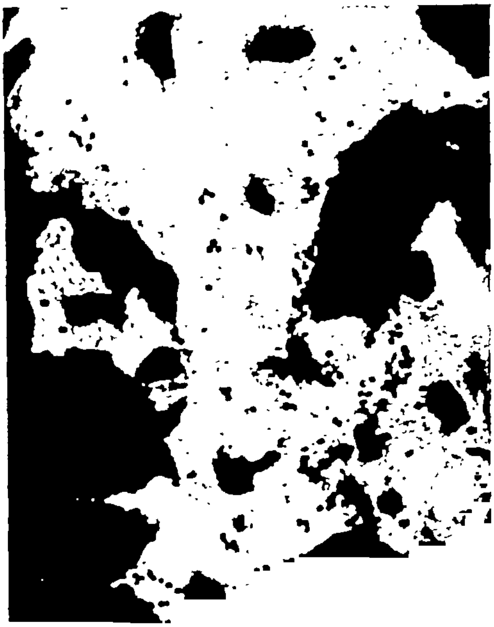

FIG. 1. Bacteria shown adjacent to a Randall plaque

In evidence that infection is the forerunner of the Randall plaque, Edward C. Rosenow, Jr., reports that he found "bacteria adjacent or near to regions of calcification in the renal papilla in 24 of 37 cases in which sections were stained

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 17, 1951.

for organisms. Of 24 papillae, not showing plaques, a few bacteria were found in only one case." See figure 1.

Keyser experimentally produced renal calculi by traumatizing the renal papillae and injecting a culture of bacillus proteus. He termed this area as necrobiotic tissue. See figure 2.

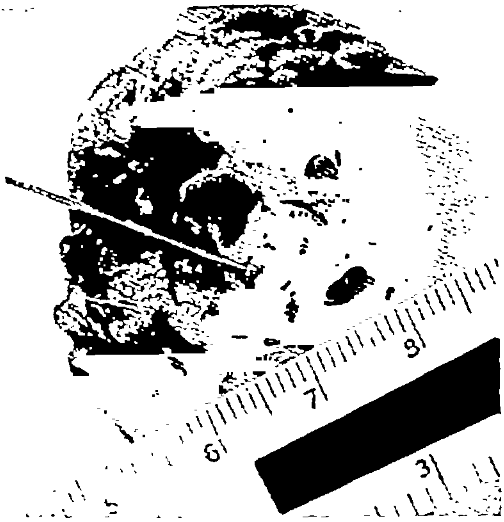

FIG. 2. Stone produced by trauma and infection of B. proteus (rabbit's kidney)

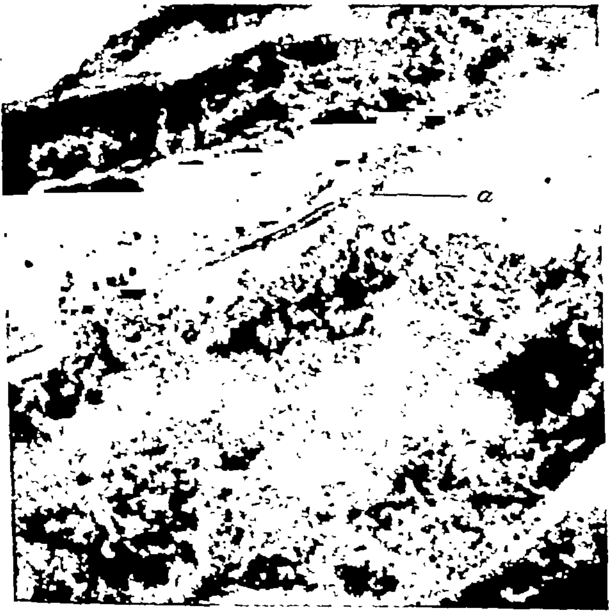

FIG. 3. Staphylococci in center of original amorphous phosphate stone

Herman recites a striking case of a 9 year old boy with osteomyelitis of the tibia, the infecting organism being staphylococci. On admission the urine was normal and 2 months later bilateral stones were found and when removed were found to have staphylococcus as a nucleus.

Hellstrom of Stockholm makes a strong case of the thesis that staphylococci provide a nucleus for stones of amorphous phosphate. He cultivated staphylococci from the center of stones and even in instances where the B. coli was cultured in the urine, staphylococci were found in the organic framework of the stones. All this would testify to the probability that stones may be formed with bacteria as the nucleus. See figure 3.

There is a paucity of information concerning the effect of bacteria on the colloids. Dr. Arthur Butt has recently revived our interest in the colloidal theory. He reported that colloidal activity is increased in the Negro and in the pregnant woman, suggesting this as an explanation of the small percentage of calculi found in these cases. He also stated that hyaluronidase apparently created increased colloidal activity in urine and when administered prevented the formation of encrustations where indwelling catheters were present.

THE ROLE OF BACTERIA IN THE RECURRENCE OF STONES

There is little disagreement concerning the part that infection plays in the recurrence of stone formation. Its occurrence is most commonly due to the urea splitting organism which causes the urea to form ammonia and carbon dioxide. This highly alkaline state changes the soluble monocalcium phosphate to the more insoluble dicalcium phosphate which always occurs in a highly alkaline urine.

We rarely see infection accompanying stones of uric acid, cystine, xanthine and oxalate (Weddellite) variety. Hammarsten experimentally produced calcium oxalate calculi in noninfected urine in rats, and this experiment was reproduced by Edward Prien. An analysis of 100 stones in our clinic revealed of 10 uric acid stones, the urine was noninfected in 8; of the 57 calcium oxalate stones, infection was absent in 40. In contrast to this all of the 24 magnesium ammonium phosphate stones were accompanied with infection. Of the 9 composed of calcium phosphate and carbonate, 7 were accompanied with infection. See table 1.

Suby states that 54 per cent of stone cases in Massachusetts General Hospital are infected and probably all the magnesium ammonium phosphate stones were due to urea splitting organisms.

Charles Higgins found that of 200 recurrent stone cases, 81 per cent were infected. These were large stones. The small noninfected stones were uric acid urates or oxalates.

The impelling conclusion is that the real factors to be considered in the recurrence of stones as far as infection is concerned are stones composed of magnesium ammonium phosphate (struvite) calcium carbonate and calcium phosphate (apatite).

The organism causing recurrence is invariably a urea splitting organism, and any other organism present is the result rather than the cause of recurrence.

It is highly important then to know what organisms have the urea splitting property.

Urea splitting properties have been ascribed to many different organisms. For example, Richard Chute reported that stones of staphylococcus, Pseudomonas aeruginosa, hemolytic influenza, diptheroids and many strains of Escherichia coli contained urea splitting faculties.

Hellstrom of Stockholm emphasized the importance of Micrococcus as a urea splitting organism.

George Gilbert Smith recognized 2 organisms as the main offenders, Micrococcus and Proteus. He is of the opinion that B. coli are of no great importance.

Albright expressed the opinion that Staphylococcus albus split the urea but that Staphylococcus aureus did not.

To clarify this problem our laboratory made a study of 332 organisms. We were able to demonstrate that practically all of the strains of Proteus vulgaris caused the decomposition of urea in urine.

TABLE 1. *Stone cases with infection*

COMPOSITION	NO.	INFECTED
Calcium oxalate	57	17
Uric acid	10	2
Cystine	0	
Xanthine	0	
Magnesium	24	24
Calcium phosphate—carbonate	3	2
Calcium phosphate	3	2
Calcium carbonate	3	3
Total	100	50

About 50 per cent of the Micrococcus had the faculty of decomposing the urea This property appeared in both the albus and the aureus, hemolytic and non-hemolytic.

Only 5 of the 51 Pseudomonas aeruginosa contained urease, and out of 99 Escherichia coli only 1 had the faculty of splitting urea. See table 2.

It would, therefore, appear that the faculty of decomposing urea in urine is practically always due to the Proteus or the staphylococcus.

The conclusion from these observations is that as far as infection is concerned our problem involves the two organisms, the Proteus and the Micrococcus, and the calculi involved are composed of the magnesium ammonium phosphate, the calcium carbonate and calcium phosphate.

This then simplifies our problem and permits us to concentrate our attack.

The enzyme urease is apparently endogenous. When we filtered urine containing urea splitting organisms through the Seitz filter the filtrate contained no urea splitting properties, thus indicating that the urease is not free in the urine but is dependent upon the presence of the organism itself.

Our first objective is to discover whether a urea splitting organism is present or not.

Hellstrom has invited our attention to the fact that many times in the clinical practice Micrococcus has been noted on the stained smear and yet not grown on the culture. We also have noted this.

Likewise the Proteus may not be properly identified in every instance because of atypical reactions.

Emerson and McIntosh presented to this association a method to avoid overlooking the presence of urea splitting organisms. They utilized a modified Van Slyke method of determining the presence and amount of activity of urease in the urine. The method may be described as follows:

Urease acts on urea in a phosphate buffer solution and the time required for the pH to rise to a definite point is observed. A photocell colorimeter is used to follow the reaction and determine the end point. The amount of enzyme present is inversely proportional to the length of time required for the pH to rise from 6.7 to 7.7 and is expressed in Sumner units. This unit is the amount of urease capable of producing 1 mg. ammonia nitrogen in 5 minutes at 20C under specific conditions.

TABLE 2. *Decomposition of urea by bacteria*

ORGANISM	NO	UREA +	UREA −
Proteus vulgaris	42	40	2
Staphylococcus pyogenes	39	19	20
Pseudomonas aeruginosa	51	5	46
Escherichia coli	99	1	98
Escherichia intermediate	16	1	15
Aerobacter aerogenes	47	0	47
Paracolon coliforme	6	0	6
Alcaligenes fecalis	14	0	14
Streptococcus fecalis	18	0	18
Total	332	66	266

We have utilized this test with good results and find it to be of value and a reliable method in determining the amount of urease capable of decomposing urea present in the urine. In practical application we have found that the test depends on the urease contained bacteria present, therefore, the specimen must be collected in an aseptic vessel and examined immediately to prevent the increase in the number of bacteria. The presence of a marked amount of pus interferes with the colorimetric readings. A few organisms picked up on culture will give a strong reading bacteriologically whereas the biochemical reading may be very slight. We personally still prefer the bacteriological determination.

TREATMENT

Proteus infections. Having established the presence of a Proteus or staphylococcus infection it is highly important to eliminate it if possible. We will concentrate our report on these organisms.

Aureomycin has proved relatively ineffective with the Proteus. The *in vitro* tests of 76 organisms showed 7 per cent were inhibited. In vivo study of 12 organisms showed 8 per cent were controlled.

Terramycin also proved ineffective. Of 44 organisms studied 7 per cent were inhibited and none were controlled in vivo. It would appear that aureomycin and terramycin are not the drugs to use in combating the Proteus infection.

Chloromycetin proved definitely more valuable. Of 78 organisms studied in the laboratory 82 per cent were inhibited. Fifty per cent of patients harboring the Proteus infection were controlled with chloromycetin. The drug would not have proved effective in some of these patients unless very large doses of chloromycetin were given initially; that is, 1 gm. every ½ hour for 3 doses. This created a blood level between 50 and 60 mcg/cc. This permitted an organism which was inhibited in the test tube to be controlled by 16 mcg/cc. No other antibiotic can produce such a high blood level by large doses.

Gantrisin also proves to be an effective agent against the Proteus. Of 53 organisms examined 68 per cent were inhibited. In vivo, 66 per cent were inhibited.

TABLE 3. *Proteus vulgaris* in vitro

	SUSCEPTIBLE	RESISTANT
Streptomycin	49	14
Aureomycin	6	70
Chloromycetin	64	14
Gantrisin	39	14
Terramycin	3	41

TABLE 4. *Staphylococcus pyogenes (micrococcus)* in vitro

	SUSCEPTIBLE	RESISTANT
Streptomycin	29	20
Aureomycin	35	5
Chloromycetin	36	3
Gantrisin	11	22
Terramycin	30	18

Streptomycin will control about 77 per cent, but its great tendency to cause the emergence of resistant strains and its awkwardness of administration and toxicity in large doses make it less desirable as a drug of choice. See table 3.

Micrococcal infections. The Micrococcus pyogenes is used here to connote the previously termed staphylococcus according to Bergey's Manual. The Micrococcus pyogenes, as stated before, may be present and not appear on culture. The gram stain should be carefully studied in all persistent alkaline urines for a Micrococcus. Penicillin can no longer be relied on exclusively for therapy. Nichols and Needham found 68 per cent of such infections isolated on the surgical service of the Mayo Clinic penicillin-resistant. Obviously these had received sublethal doses previously. Our study indicates aureomycin and terramycin are highly effective against these penicillin-resistant strains. We recommend the use of large doses of penicillin first and if found ineffective, aureomycin should be given. See table 4.

Arsphenamine, .3 gm. given intravenously every other day for 3 doses, is sometimes dramatic in its effect. The urine from nephrostomy tubes and splinting urethral tubes should be re-examined frequently for alkalinity and staphylococci and Proteus infections and quickly and vigorously treated. Suby's solution and versenate have proved helpful as a continuous irrigating solution and possibly hyaluronidase may be helpful in preventing encrustations.

Sensitivity tests of the infecting organism are essential in the stubborn cases. We have many cases illustrative of the fact that often only one antibiotic came within the inhibition range.

Infection due to the presence of stone. Heretofore our discussion has been confined to the organisms which caused stone formation. Many organisms are present because of the stones. The primary treatment of these infections is surgical drainage and will be discussed by other essayists.

The organisms present as secondary invaders are most commonly Escherichia coli, Pseudomonas aeruginosa, the Aerobacter aerogenes and Streptococcus fecalis.

Escherichia coli are the most common and likewise the most easily controlled by any of our known drugs. Mandelamine or gantrisin is usually effective.

Pseudomonas is the most resistant and as yet there is no nontoxic antibiotic that will inhibit all the strains. Terramycin is probably the drug of choice since we found that of 63 organisms studied, 44 per cent were inhibited. The gantrisin and chloromycetin are notably ineffective.

Aerobacter aerogenes is best treated with terramycin and aureomycin. Streptomycin, chloromycetin and gantrisin are relatively of little value.

Streptococcus fecalis is successfully treated with mandelamine or aureomycin and chloromycetin. Gantrisin is of little value with this organism.

SUMMARY

The role of bacteria in nephrolithiasis is an important one. The organisms involved in the formation or reformation of renal stones are the urea splitting organisms; the Proteus and about 50 per cent of the Micrococcus pyogenes. The stones formed are usually of the struvite or apatite variety; that is, the magnesium ammonium phosphate, the calcium carbonate and the calcium phosphate stones. Infection does not play a major role in the formation of uric acid, urate, xanthine and oxalate stones. Bacteria may play an important role as a secondary invader resulting from obstruction by a stone. These should be controlled when surgical relief is undertaken.

The treatment for the Proteus infection is chloromycetin in large initial doses and gantrisin.

The Micrococcus pyogenes is best treated by penicillin, but there are many penicillin-resistant strains. Terramycin and aureomycin are often effective against these resistant strains.

Drug therapy is suggested for the secondary invaders such as the Pseudomonas aeruginosa, the Aerobacter aerogenes, the Streptococcus fecalis and others.

The careful identification of the infecting organism, the application of sensitivity tests and the drug of choice will appreciably reduce the morbidity and increase the probability of successful treatment of nephrolithiasis.

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DISSOLUTION OF URINARY CALCULI

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During the past 13 years much work, relevant and irrelevant, has been done in the laboratory in an attempt to find an efficient yet safe method for dissolving urinary stones. Many interesting and valuable findings have been made, but the solutions thus far concocted have been proved by us to still be impractical in most cases. The fundamentals for treatment of urinary stones have not been changed. Dissolution is definitely the addendum, not the epistle. It is still the side show.

The stone dissolution problem can best be divided into two considerations: 1) theoretical consideration; 2) practical consideration.

THEORETICAL CONSIDERATION

The theoretical problem envisions the stone—chemical substance—in equilibrium with the solution in which it is immersed. This solution may be water, acid, alkali, or salt. In vivo, of course, the stone is in equilibrium with the complex components of the urine. The theoretical principle of stone dissolution is to cause increasing ionization of the stone. Stone ions, adrift in the solution at all times, can be captured by other appropriate ions yielding a soluble product, thus forcing the stone (which must keep up the equilibrium) to give more and more ions and dissolve.

A. Calcium phosphate (including magnesium ammonium phosphate and calcium carbonate). In the case of calcium phosphate, the addition of any acid solution provides hydrogen ions and "radical" ions to act as the procurement forces. The hydrogen ions attach themselves to the phosphate ions producing soluble phosphoric acid, and the "radical" ions attach themselves, in various degrees of efficiency, to the calcium ions thus making this part of the stone also soluble. Strong inorganic acids with low pH such as HCl, H_2SO_4, etc. do well but are obviously too iritating to be practical. The value of citrate as an efficient "combiner" with calcium has been known for many years. It is the basis for the use of citrate as a substance to prevent the clotting of blood. A soluble complicated calcium citrate molecule is formed, and this was the rationale for our earlier studies in stone dissolution.

By measuring loss in specific gravity of rabbits' teeth (calcium phosphate) immersed for 8 hours in solutions of different chemical composition, concentration, and pH—an index of efficiency for approximately fifty organic and inorganic acids was established. By testing living rabbits' bladders with all of these solutions it was likewise possible to establish an index of irritation. By pure chance it was noted that certain solutions were rendered much less irritating but no less efficient by the addition of magnesium. This finding led us to

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 17, 1951.

propose solution G and solution M as feasible solutions for certain practical usage. The formula for solution G (pH 4) is:

Citric acid (monohydrate)	32.25 gm.
Magnesium oxide (anhydrous)	3.84 gm.
Sodium carbonate (anhydrous)	4.37 gm.
Water	1,000 cc.

During the time that this experimental work was being conducted, we were also making many experiments with certain water softeners. Calgon (still recommended for automatic dishwashers today) was found to be about equal to solution G in its ability to dissolve calcium phosphate, but it was found to be much more irritating. Moreover, it was impossible to lessen its irritation by adding magnesium.

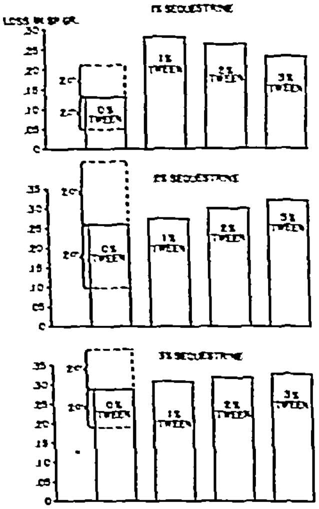

FIG. 1

Our interest in water softeners continued, however, and after World War II in Dr. Fuller Albright's laboratory we did much experimental work with sequestrine (versene acid, ethyl diamine tetra acetic acid). This was supplied to us by the Alrose Chemical Company of Providence, Rhode Island and their Mr. Zussman gave us much advice regarding its use. This was the same substance (calsol) that was reported by Dr. Gehres and by Dr. Abeshouse at the 1950 meeting of the American Urological Association. The results of our experiments with this acid were encouraging but in strengths of good efficiency, sequestrine was found somewhat more irritating than solution G. We have continued and are continuing our work with this solution.

In an attempt to speed dissolution, wetting agents have been added to the solvents. Wetting agents, used in detergents, theoretically bring the solvent closer to the solute. Tween 80, a wetting agent made by the Atlas Chemical Company, enhanced the solubility effect of sequestrine in our first experiments. This was especially marked with the 1 per cent sequestrine solution and sent our hopes high (fig. 1). Later and more carefully controlled experiments, however, failed to confirm these results. Other wetting agents are being considered for it certainly seems that this phase of the work may be of great importance.

B. Calcium oxalate. Calcium oxalate stones are about the most prevalent primary urinary stone, and they are also often the hardest and the most difficult to attack by dissolution. Solution G has very little effect on them. It is a fact that versene acid does have more effect on calcium oxalate stones than does solution G. This is shown in figure 2. It is noted that the weight of calcium oxalate stones immersed in 2 per cent sequestrine definitely decreases. The graph looks encouraging but this amount of dissolution is impractical. Unless a stone of this comparable weight is completely dissolved in 50 to 75 hours, we have learned that the solvent used is relatively impractical. We have speculated regarding the use of bacteria or ferments on oxalate stones. Agricultural chemists tell us that certain soil bacteria grown on media containing oxalic acid will and do ultimately dissolve oxalate, but Father Time may be too slow for a patient with a renal stone. Some encouraging experiments using ferric chloride solution as the solvent have been conducted. This is still in the impractical stage, however.

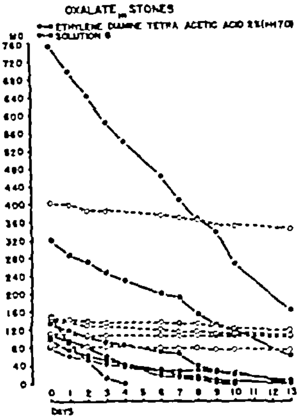

FIG. 2. Weight of calcium oxalate stones immersed in 2 per cent sequestrine solution and in solution G.

URIC ACID

Uric acid stones and crystals have been subjected to many types of alkaline solutions (sodium hydroxide, sodium bicarbonate, sodium borate, lithium borate, etc.) but results so far have suggested that the dissolution effect of each of these solutions has been dependent upon the pH. The higher the pH of the solution the more efficient the solubility effect on uric acid. Gehres reported that versene acid had good solubility effect on all stones. We have been unable to substantiate that. Figure 3 shows the decrease in weight of uric acid stones immersed in 2 per cent versene acid (pH 7.0) for 14 days. The same figure shows that uric acid stones immersed in a buffered watery solution at pH 7.0 dissolved just as rapidly (precisely the same rate) as did those in versene acid. The pH of the solution again seems to be the important factor.

Whereas it is usually improbable that alkalinization of the urine will cause dissolution of uric acid stones in patients, it is becoming better established that this form of therapy is of unquestionable importance in preventing further formation of uric acid stones. We usually advise a low purine diet plus sodium citrate—two grams four to six times a day, and have the patient test his urine with nitrazine paper to keep the pH at 7.5.

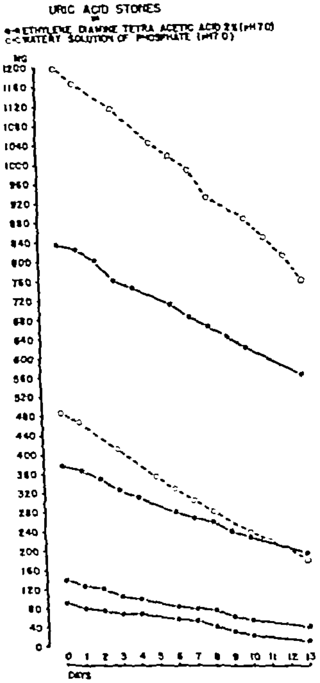

Fig. 3. Weight of uric acid stones immersed in 2 per cent sequestrine (pH 7.0) and in a buffered watery solution at pH 7.0.

CYSTINE STONES

What has been stated regarding the dissolution of uric acid stones applies in essence to the problem of dissolution of cystine stones. So far we have found no good solvent for cystine that has not been extremely alkaline. A solution at pH 10 is much more effective than one at pH 9. This is shown in figure 4. We do feel that alkalinization of the urine is advisable in these patients to help prevent recurrence.

PROTEIN MATRIX

Attack on the protein matrix, although important, is probably of less importance than attack on the inorganic stone substance. If the inorganic salts are dissolved—the castle usually crumbles and piece by piece is washed away. By dissolving "sludge," however, it is possible that inorganic salts are for the first time exposed to the inorganic solvent. Experiments with many proteolytic enzymes have been done, but these have not produced convincing results. Inactivation of enzymes at certain pH levels has made their use impractical with many solutions. We have recently done experiments using desoxyribonucleoproteinase (dornase) on urinary sediment. Dornase has been proved a good proteolytic enzyme for dissolving pleural effusions etc. by Tillets et al. of New York City. We have used the Feulgen stain to test the solubility effect (fig. 5). Our practical problem of course is different from that of a closed pleural space where dornase can be locked and kept dormant for many hours at a time.

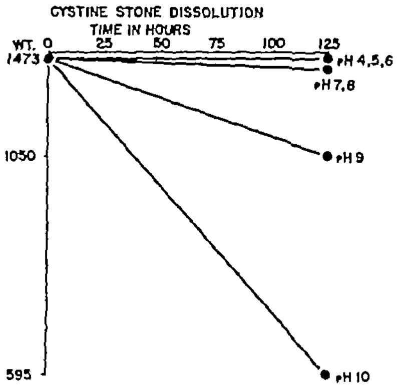

FIG. 4. Weight of cystine stones in buffered solutions of different pH levels

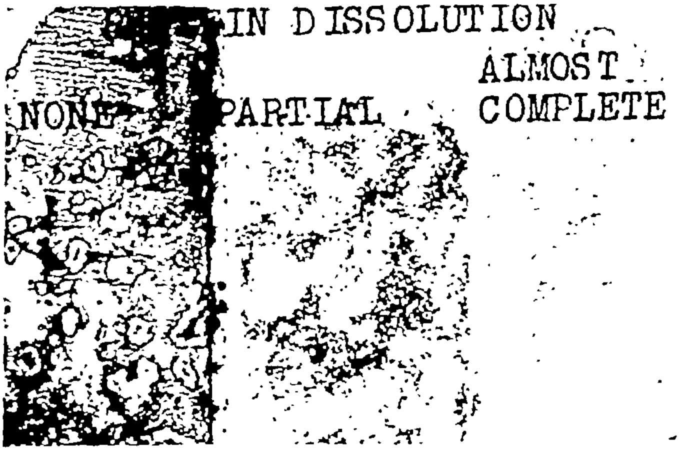

FIG. 5. Feulgen stained specimens treated with dornase

We are working in a moving stream, and this enzyme may be washed away before it can do its magic.

PRACTICAL CONSIDERATION

Time and space preclude the possibility of our discussing the entire problem of mechanically getting and keeping the solution in contact with the stone. As we have stated previously, this will usually be dependent upon the patience and ingenuity of the attending urologist. Simplicity is of greatest importance, however, if the patient is to do his own irrigating, and the shortage of nurses and attendants have usually necessitated this plan.

There are two simple basic methods of irrigation which can be utilized. The first entails running a constant flow of solution through an inlet tube and allowing its constant escape from the kidney or bladder through an outlet tube. There are two main objections to this method. The first is that it requires a large amount of solution which actually does not do its full capacity of work. This is expensive and bulky. The second objection is that there is a good possibility that the stone is only partially touched, or even completely missed, by the migrating solution which is constantly seeking the route of least pressure and eventually the outlet tube. In other words, there is danger of the "magenstrasse" effect. By raising the outlet tube some of this bad effect can be eliminated.

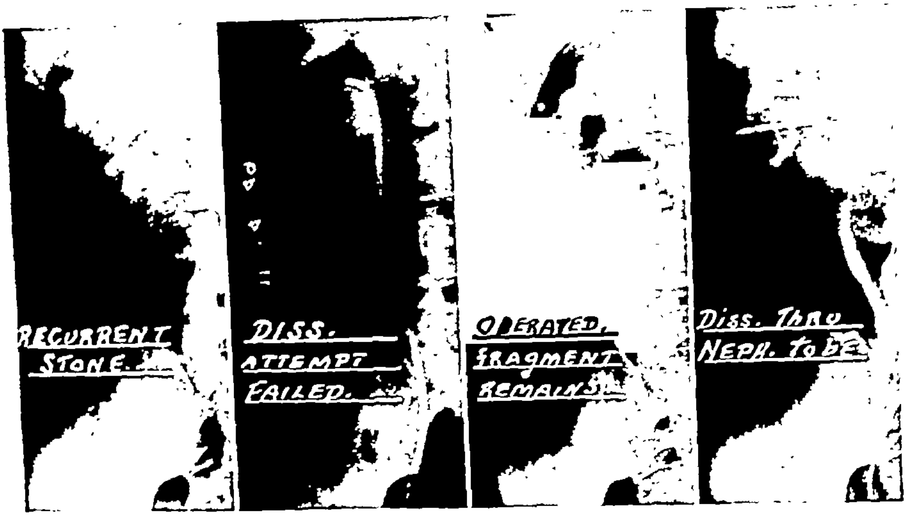

Fig. 6. Case 1

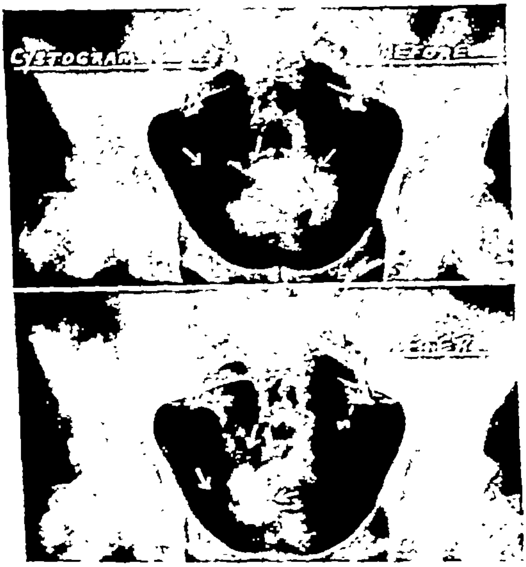

Fig. 7. Case 2

The second method of irrigation is the intermittent closed type which allows a certain amount of solution to enter the kidney or bladder, locks it there for a certain length of time, then allows it to drain for a specified period of time. Although this method has the disadvantage that the solvent is diluted by the urine excreted during the "locked in" period, it has the advantage that it insures that the stone is surrounded by the solution. It also has the advantage that it allows spells of complete rest for the kidney or bladder—a fact of great importance in preventing fever, pain, or bleeding. We have preferred this second method.

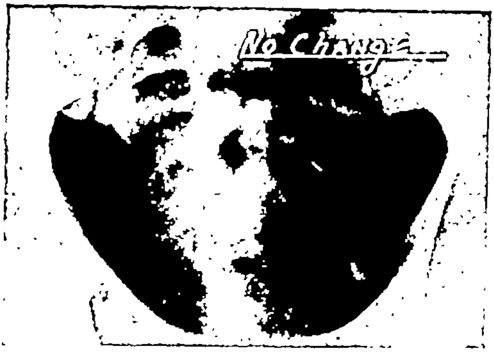

FIG. 8. Case 3

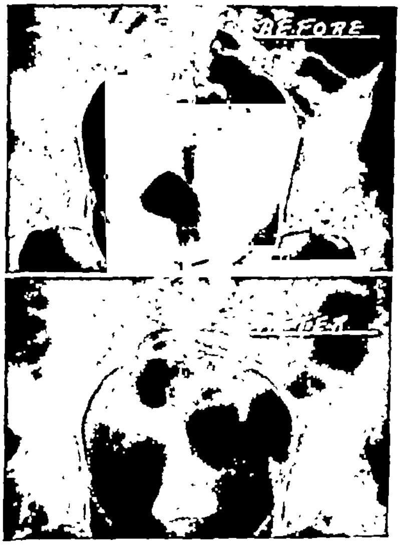

FIG. 9. Case 4

Seven cases who have had trials of irrigation with 2 per cent versene acid are presented. This is obviously a preliminary report, but it is timely.

Case 1 (fig. 6): A 37 year old man with recurrent right renal stones attempted dissolution with solution G through a ureteral catheter; this was unsuccessful. Right nephrolithotomy was done but two small fragments were left. Sequestrine

(2 per cent) irrigations through a nephrostomy tube were tried but caused the patient such severe pain that they had to be omitted. Solution G irrigations caused patient no pain.

Case 2 (fig. 7): A 72 year old man with 3 nonopaque bladder stones was irrigated intermittently with 2 per cent sequestrine. He had very severe pain, and after a few days the stones were removed by suprapubic cystostomy. There had been no evidence of dissolution.

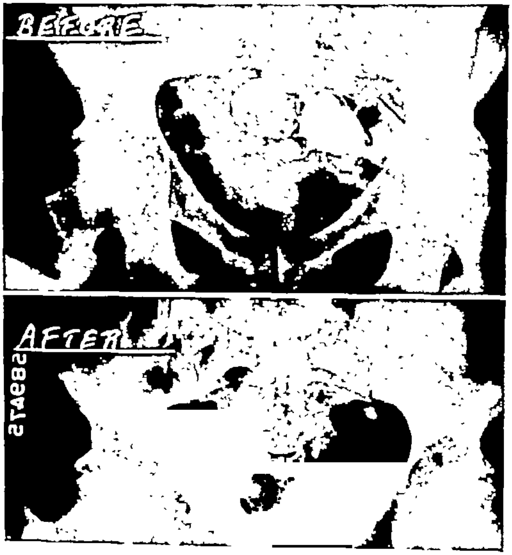

Fig. 10. Case 5

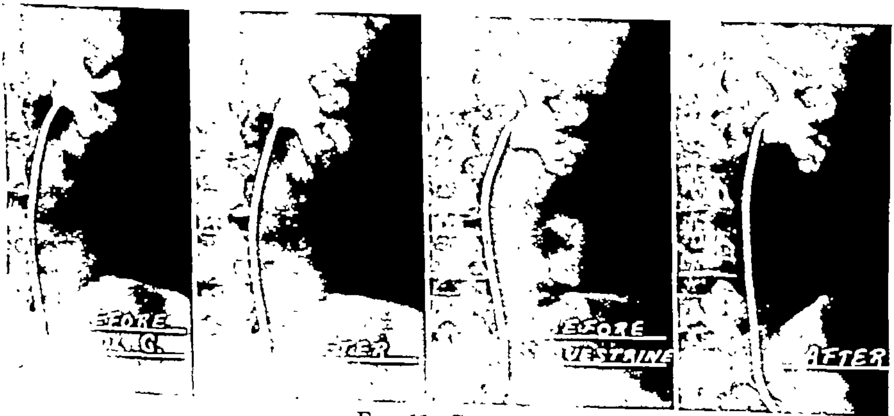

Fig. 11. Case 6

Case 3 (fig. 8): A 70-year-old man with a single bladder stone attempted dissolution by intermittent irrigation with 2 per cent sequestrine. He had so much pain that only a few hours of irrigation could be tried. Dissolution with sequestrine was obviously impractical, and his stone was removed surgically.

Case 4 (fig. 9): A 30-year-old paraplegic with a single large bladder calculus used intermittent irrigations of 2 per cent sequestrine, but fever and bleeding occurred. Sequestrine 1½ per cent was tolerated better, and the stone became smaller. She is continuing irrigations at home.

Case 5 (fig. 10): A 71 year old man with two bladder stones attempted dissolution with 2 per cent sequestrine but the pain was intolerable. The stone was removed surgically.

Case 6 (fig. 11): A 39 year old woman with bilateral renal stones showed no evidence of dissolution with solution G through a ureteral catheter. She was then irrigated with 2 per cent sequestrine solution, but the pain was intolerable. Irrigations with 1½ per cent sequestrine were then done 6 or 7 hours daily for 10 days, but there was no evidence of dissolution.

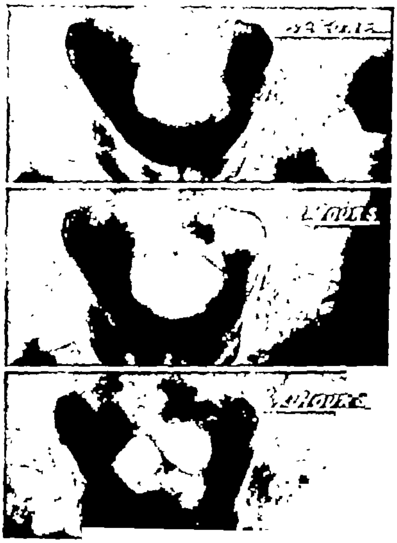

FIG. 12. Case 7

Case 7 (fig. 12): A 54 year old paraplegic with four large bladder calculi was irrigated intermittently with 2 per cent sequestrine solution. He tolerated the solution poorly, voiding it around his catheter, and in spite of his paralysis, experienced pain in the bladder and legs. The stones were removed surgically.

Whether or not this small group of cases had unusually sensitive bladders and kidneys is questionable, but the trials did seem to indicate that 2 per cent sequestrine was quite irritating and very painful. Our laboratory technicians have noticed this fact also—complaining of severe pain if they accidentally got a little sequestrine onto a crack or cut in their hands.

No one knows more of the trials and tribulations of stone dissolution than do those who have spent time working on the problem. By subjecting our failures to careful scrutinization we are attempting to better our judgment and techniques. The problem is extremely interesting and should gain in practical importance as more careful work is done, but it is a long and difficult problem. It is still the sideshow.

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URINARY CALCULI ASSOCIATED WITH NEPHROCALCINOSIS

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The formation of urinary calculi frequently accompanies or follows abnormal renal calcification of the type described as nephrocalcinosis. In an earlier review of 7 cases of nephrocalcinosis, 5 were reported as having stones.[1] In the past year 5 additional cases have come to my attention and all were associated with calculus formation.

In the earlier report all cases presented diffuse bilateral calcifications which were demonstrated by roentgen examination. However, observation of subsequent cases indicates that the disease may be unilateral or even segmental, involving only a portion of a kidney.

In using the term nephrocalcinosis it should be emphasized that it implies no uniform etiology. In a recent review of the subject Vaughan, Sosman, and Kinney[2] point out that abnormal calcification may result from 1) abnormally high concentrations of calcium or phosphorus in the blood with resulting precipitation of calcium phosphate in normal tissue or 2) local tissue damage with precipitation of calcium in the presence of normal blood levels. The former condition is exemplified clinically by cases of hyperparathyroidism. The experimental production of renal calculi by excess feeding experiments, the "hyperexcretion stones" referred to by Keyser, appears also to belong in this category.

The second classification may include a wide variety of conditions, in fact, any condition associated with renal cellular damage. Infections, bacterial toxins, and many chemical agents are known to damage renal cells and therefore may initiate tissue injury followed by calcification. Among the chemical agents, the sulfonamides are apparently causative in many cases as shown by evidence presented previously.[1–3]

Vaughan, Sosman, and Kinney[2] also call attention to the fact that abnormal calcification is more likely to occur where pronounced changes appear in the pH of the media or where there is an increased concentration of phosphatase. Thus the renal tubules with cells high in phosphatase and where there are marked changes in the pH of the media prove an ideal location for calcification.

Many of the cases of nephrocalcinosis have been associated with hyperchloremic acidosis. Albright[4] and his co-workers believed this was due to disease of the distal convoluted tubules, the systemic acidosis having occurred because the kidney was unable to produce ammonia and to excrete acids. The shortage

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 17, 1951.

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of base by which acids are excreted results in an increased loss of calcium in the urine to act as base. This condition can create a local metabolic state favorable for calcification of damaged renal cells.

More recently Latner and Burnard[5] studied 6 cases of hyperchloremic renal acidosis in children. Their investigations indicated that the kidneys were able to secrete free acid and to produce ammonia. They concluded that failure of absorption of bicarbonate in the proximal tubules was the primary cause of difficulty and that calcifications and other changes observed in the distal and collecting tubules result from the hypercalcinuria and chronic acidosis. It is interesting to note that only one of their cases presented the typical x-ray findings of clustered renal calcifications while another with negative x-ray findings disclosed well-marked nephrocalcinosis at autopsy.

Not all cases of nephrocalcinosis are associated with elevated blood chloride and low CO_2. Boyd and Stearns (cited by Vaughan)[2] reported a case of chronic acidosis and rickets which they believed due to renal tubular inability to produce an acid urine; however no renal calcification could be demonstrated. This is additional evidence for the opinion that the renal calcification is secondary and is the result or subsequent development of the renal tubular damage from whatever cause.

Considerable experimental work has shown that calcification follows toxic tubular damage. Randall[6] demonstrated that the kidney excretes and concentrates bacterial toxins. Injections of a streptococcus toxin caused localized epithelial damage most pronounced in the collecting tubules and tip of the renal papilla. Injections of a chemical toxin—uranyl acetate—produced necrosis of the convoluted tubules with extensive deposits of calcium salts in the necrotic epithelium. Keyser[7] obtained a B. pyocyaneus culture from a patient with bilateral renal stones. Injection of this organism killed rabbits by producing hemorrhagic tubular nephritis while a diluted filtrate produced an aseptic nephritis with terminal tubular calcifications. In two instances small microliths were found which were composed of calcium carbonate and phosphate. The calcifications were at the tips of the pyramids. Keyser also produced stones by artificially traumatizing the renal pyramids and inoculating the area with urea-splitting Proteus organisms. It is to be noted that both of the last mentioned experimental workers observed the chief changes in the collecting tubules and renal papilla although calcification also occurred in the convoluted tubules. This finding coincides with the histologic examination of human kidneys where nephrocalcinosis has been present.

Having considered the theoretical and experimental background let us explore the clinical features of this problem. My interest in this condition was aroused by the case of a 4 months' old baby boy included as case 1 in the earlier report.[1] He had an acute toxic nephritis with oliguria, hematuria and azotemia (urea 84 mg. per cent). The history strongly indicated a reaction to sulfonamide medication. As the child improved, there was return of normal glomerular function and normal blood urea. Evidence of tubular damage persisted, however. He had a mild acidosis with elevated blood chloride, polydipsia, polyuria and hyposthenuria. A subsequent roentgenogram of the kidneys revealed bilateral diffuse, minute, faintly visible calcification which occurred in clusters corresponding with the renal lobules. He was observed periodically for the following 19 months, during which time the renal calcifications became progressively more pronounced and he began passing small calculi (fig. 1, *A*). During this time the child appeared to develop normally and there was no radiologic evidence of bone change.

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[5] LATNER, A. L. AND BURNARD, E. D.: Quart. J. Med. **19:** 285. 1950.

[6] RANDALL, A.: Internat. Abstr. Surg. **71:** 209, 1940; in Surg. Gynec. & Obst., 1940. RANDALL, A.: J. Urol., **44:** 580, 1940.

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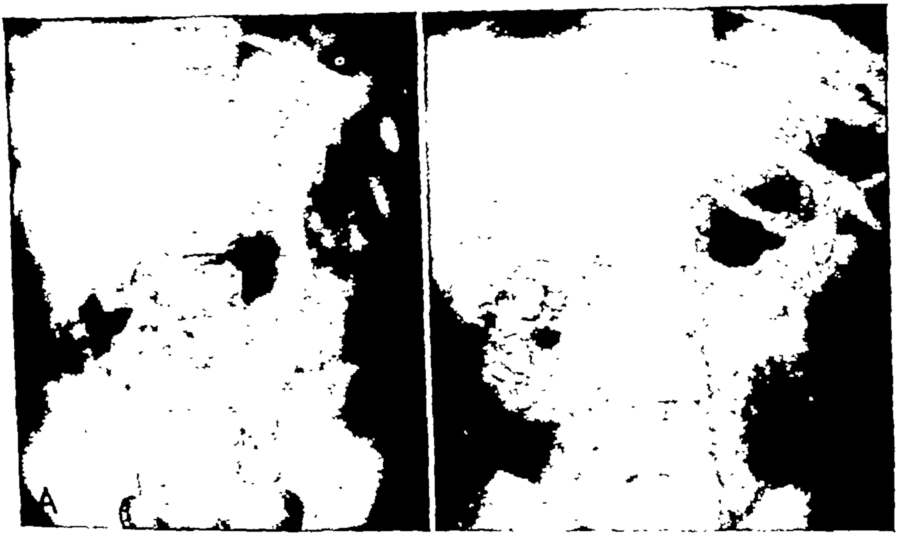

FIG. 1. *A*, Plain roentgenogram showing multiple clustered calcifications occurring in child of 19 months after acute toxic nephritis. *B*, plain roentgenogram of 2¼ year old brother of patient shown in *A*. Note bilateral nephrocalcinosis and multiple calculi in right renal pelvis.

Shortly after the discovery of the nephrocalcinosis in this child the mother related that a son aged 2½ had been passing stones. At my request the boy was examined and extensive bilateral nephrocalcinosis was found with multiple stones in the right renal pelvis (fig. 1, *B*). He also had polydipsia and polyuria with enuresis and the specific gravity of the urine was never observed to be above 1.012 (early morning specimen). He had developed normally and there was no radiologic evidence of rickets. The history in this case indicated renal injury, probably the result of an early treatment with sulfa drugs. At that time the mother had noted "red urine". This was not a familial disease as indicated by the fact that roentgen examination of the kidneys of all other members of the family revealed no suggestive calcifications.

The relationship between the nephrocalcinosis and the development of calculi in these children appeared to occur in the following sequence: toxic renal injury followed by calcification in the tubules and papilla, progressing to stones in the renal pelvis. As previously stated, 5 of the 7 patients who formed the basis of the earlier report had passed stones and the sequence of events followed a similar pattern.

Interest in this subject brought other cases to our attention and we discovered previous cases seen at the clinic in which the true nature of the problem had not been recognized. In this connection I think it pertinent and instructive to relate that, on the basis of the radiologic findings, 2 of the cases had been mistakenly diagnosed as renal tuberculosis, an understandable error since the type of calcification may in some cases be almost identical.

A summary of the histories of the additional cases of nephrocalcinosis associated with calculi follows:

Case 1. A man aged 47 was first seen at the Clinic in January 1944, complaining of pain in the back and sciatica. He had been ill for about 3 months and, associated with the discomfort in the back, had experienced pain in the hip. Previous to the development of the present symptoms he had had an otitis media followed by a draining ear. The most significant finding on examination was the presence of an indurated, tender mass in the right flank. The white blood count at that time was 26,850, with 3,870,000 red blood cells and 74 per cent hemoglobin. The blood urea was 96 mg. per cent, which on recheck examination three days later, was 81 mg. per cent. The tender mass in the right flank was thought to be an abscess, probably a psoas abscess. Plain film of the abdomen showed some obliteration of the right psoas shadow. There were multiple small pinpoint-sized calcifications diffusely scattered through both kidney areas (fig. 2). The possibility of renal tuberculosis was considered, but tubercle bacilli could not be demonstrated on repeated examinations of the urine.

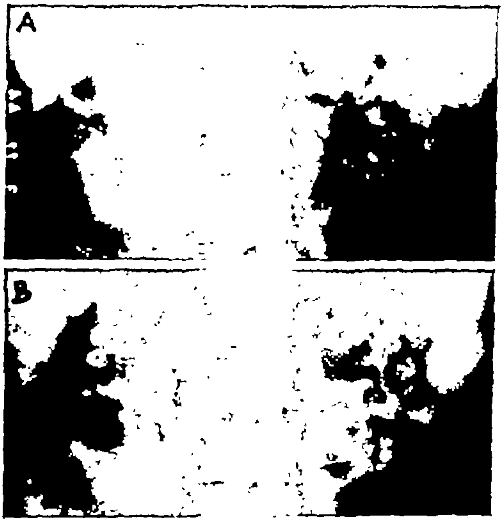

FIG. 2. *A*, plain roentgenogram and *B*, excretory urogram of case 1 made soon after original visit. Note very fine renal calcifications occurring distal to calyces.

On February 10, incision and drainage of a large abscess in the right flank was performed. Smears and culture of the pus were negative for tubercle bacilli but the culture yielded a growth of Staphylococcus albus. The patient improved significantly but a roentgenogram on March 11, 1944 showed more extensive renal calcifications. On May 5, 1944 a recurrent abscess became manifest in the right flank which was drained surgically. Since it was superficial it was not judged to be a perinephric abscess.

The patient was next seen in February 1945, at which time a roentgenogram of the abdomen revealed extensive bilateral renal calcifications. In December 1945, he experienced gross hematuria and at that time passed a calculus. In April 1946, a recheck film of the kidneys revealed a decided increase in the renal calcifications and the patient gave a history of having passed additional stones, many without exceptional discomfort (fig. 3).

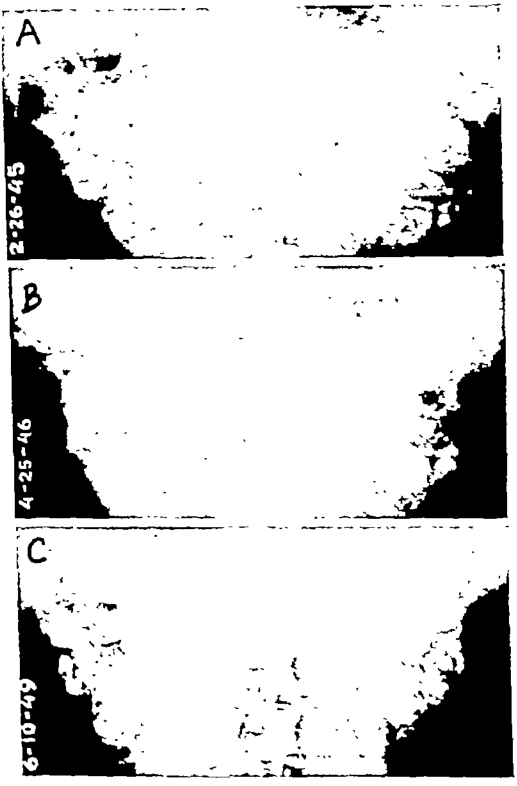

Fig. 3. Showing progressive increase in renal calcifications, case 1. Dates shown on each film.

He was examined again in June 1949, at which time there was further increase in the amount of renal calcifications and numerous shadows evident in the region of the kidney pelves. An excretory urogram showed limited excretion of diodrast and the kidney pelves were not visualized.

He was next seen in September 1950, when he was admitted as an emergency case because of complete urinary retention due to a stone impacted in the urethra. Efforts to extract this calculus failed and it was finally pushed back into the bladder and removed by litholapaxy. At this time the blood urea ranged between 74 and 87 mg. per 100 cc. A roentgenogram revealed significant increase in bilateral renal calcification. The left ureter was dilated and was completely filled with multiple small and large stones (fig. 4). The patient's general condition had deteriorated and surgical intervention was considered unwise.

In December he was admitted as an emergency case to another hospital because of ureteral obstruction on the right produced by a calculus. A ureterolithotomy was performed following which the patient became uremic and died. Permission for autopsy was not granted.

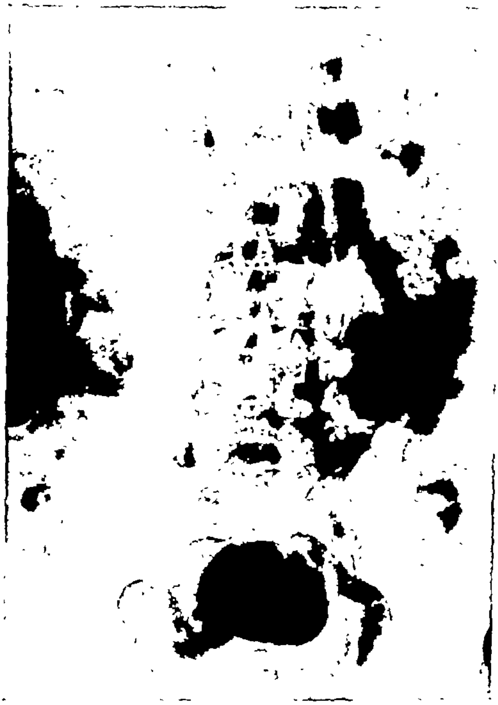

FIG. 4. Case 1. A late film showing extensive bilateral nephrocalcinosis with many calculi impacted in lower and midportion of left ureter.

The cause of the initial kidney injury in case 1 is uncertain, although it was probably due to a pyelonephritis secondary to otitis media. The case is particularly instructive, however, in that it clearly shows the progress of even minimal renal calcification to extensive disease associated with bilateral stone formation and ureteral obstruction.

Case 2. A man 26 years of age was first observed in February 1940. He had experienced hematuria 5 days previously, followed by colicky pain in the right flank which was not relieved by hypodermic injection. The pain gradually subsided, however, leaving a residual soreness in the side. He stated that seven years previously he had experienced a similar attack of acute pain in the right flank which had been relieved by a hypodermic. He was uncertain whether or not a stone had been passed at that time.

The general physical examination was without significant positive findings. Urinalysis revealed a specific gravity of 1.015, pH 5.6, a faint trace of albumin but no sugar. Microscopic examination showed 10 to 12 red blood cells and an occasional white blood cell. The blood urea was 42 mg. Plain roentgenogram of the abdomen revealed many small clustered calcifications in the right kidney region and a small cluster in the region of the midportion of the left kidney. An excretory urogram disclosed prompt excretion of the dye and both kidney pelves appeared normal. The calcifications were evident in the renal pyramids distal to the calyces. No ureteral obstruction was demonstrated. It was assumed that the patient had passed a ureteral stone and there were no operative indications at that time.

He was next examined in November 1945, on the recurrence of right renal colic associated with gross hematuria. X-ray examination again revealed the parenchymal calcifications in both kidneys and a shadow in the course of the right ureter. An excretory urogram revealed hydronephrosis of the right kidney pelvis with obstruction in the midureter due to a right ureteral calculus.

Cystoscopy was performed under anesthesia; the right ureter was dilated and the stone manipulated. Several days following this procedure the patient passed a calculus.

He was observed again in December 1946, because of a rather typical left ureteral colic. Roentgenogram showed, in addition to the bilateral renal calcifications, a shadow in the region of the lower left ureter. An excretory urogram revealed a stone well down in the left ureter productive of some ureteral dilatation. Because of its small size management was conservative and the calculus passed spontaneously.

The patient had a recurrence of left ureteral colic in February 1950, and a stone at the lowermost end of the ureter was removed by cystoscopic ureteral meatotomy and extraction. On this examination the urea was 33 mg., the kidney functional test 84 the first hour and 75 the second hour. The chemistry at this time showed a CO_2 of 57 vol. per cent, chlorides 561, calcium 11.0 mg. and phosphorus 3.7. Analysis of the stone disclosed a calcium oxalate calculus.

The urine cultures were repeatedly sterile and at no time were tubercle bacilli found. The patient has not returned for observation.

Case 2 is of particular interest as it represents an instance in which the lesion of nephrocalcinosis is not a diffuse bilateral disease. On the left side the calcification was limited to a single renal papilla and pyramid. Also, the kidney functional studies were virtually normal. There was no abnormality in the chlorides or CO_2 combining power and the patient apparently had sufficient normally functioning renal tissue to maintain these values at average levels.

Case 3. A man aged 45 was first seen at the Clinic in January 1951. Three weeks previously he had experienced acute left ureteral colic lasting several hours and requiring a hypodermic. He believes he later passed a stone, although it was not recovered. X-ray examination revealed numerous clustered calcifications in the left renal area (fig. 5).

The past history disclosed the fact that in the fall of 1949 he had an acute "strep throat" for which a sulfa drug was prescribed. As a result he developed an acute sensitivity with an exfoliative dermatitis and the drug was promptly discontinued. He recalls no urinary symptoms.

Physical examination revealed no significant positive findings. Urinalysis: pH 6.0, specific gravity 1.009 to 1.014, a trace of albumin, sugar negative. Microscopic examination of the sediment showed 10 to 12 red blood cells and 8 to 10 white blood cells. The blood chemistry studies showed a blood urea of 27 mg. and blood sugar 85 mg. per 100 cc. CO_2 combining power 56.7 vol. per cent. Chlorides 627 mg. per cent, calcium 11, phosphorus 3.8 mg. per cent.

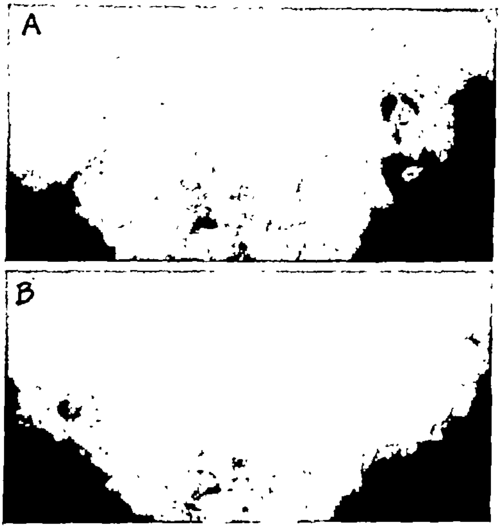

FIG. 5. Case 3. *A*, plain roentgenogram and *B*, excretory urogram showing unilateral nephrocalcinosis.

X-ray examination: Plain film showed many calcifications in clusters in the left renal area. An excretory urogram revealed satisfactory excretion of dye. The renal pelves appeared normal. The calcifications on the left side were in the pyramids adjacent to the calyces. Diagnosis: Unilateral nephrocalcinosis, left, with calculi.

Case 4. A woman aged 32 was first seen at the Clinic in January 1948, complaining of kidney stones. She had first developed pain in the left flank in 1943. X-ray at that time was reported as having shown a staghorn calculus in the left kidney. A letter from the attending physician stated that no calcifications were evident in the right kidney. Because of recurrent left renal colic and infection, a left nephrectomy was performed in July 1944. Following this operation the patient received extensive sulfonamide medication but does not recall that this was associated with ill effects.

In the spring of 1946 she had an attack of right ureteral colic and passed a stone. X-ray examination revealed the presence of multiple miliary calcifications in the remaining right kidney (fig. 6). Since that time she has frequently passed calculi which, on analysis, were found to be composed of calcium phosphate. Blood chemistry and phosphorus levels have been repeatedly within normal levels and hyperparathyroidism has been excluded. Urea clearance kidney functional test at the time of the first examination was reported as showing 74 per cent the first hour and 73 per cent the second hour. Subsequent blood chemistry studies have indicated the development of mild acidosis.

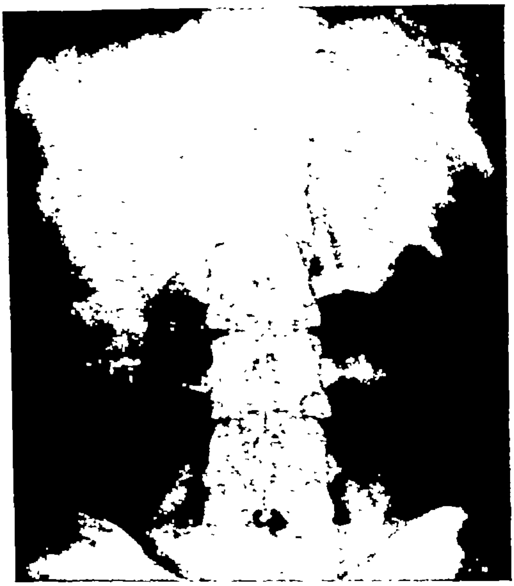

FIG. 6. Case 4. Plain roentgenogram showing typical nephrocalcinosis in a single remaining kidney.

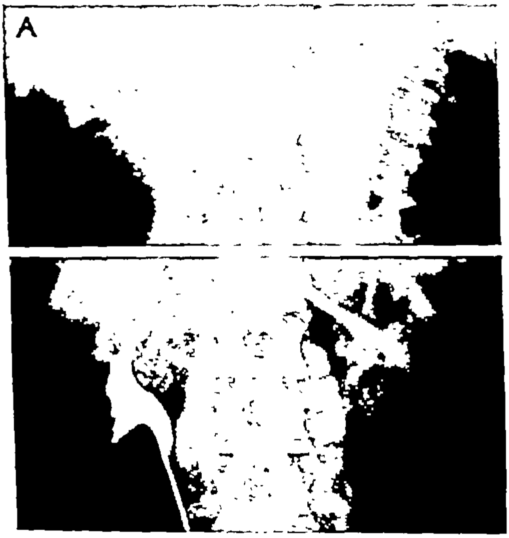

FIG. 7. Case 5. *A*, plain film and *B*, retrograde right pyelogram showing nephrocalcinosis localized to region of upper calyces.

In September 1950, the CO_2 combining power was 38.1 vol. per cent, in April 1951, 37.2 vol. per cent, and the plasma chlorides 627 mg. per cent.

Since in recent months the patient has been managed by the administration of a citrate mixture and low salt diet, x-ray examination indicates a reduction in the extent of renal calcifications, although not striking as yet.

Case 5. A man aged 45 was first seen in the Medical Department in November 1942, complaining of exceptional fatigue, exhaustion, and spells of weakness. He had also experienced recurrent attacks of renal colic associated with hematuria and the passing of stones which had occurred intermittently for the past 8 years. Previous x-ray examination had been reported as showing "gravel" in the kidney.

The physical examination was without significant positive findings. The blood pressure was normal. A plain roentgenogram of the abdomen disclosed the presence of multiple, small, irregular calcifications limited to the upper pole of the right kidney (fig. 7). A cystoscopic examination revealed no abnormality in the bladder. The right ureter was catheterized and retrograde pyelogram showed a normal kidney pelvis. The calcifications previously observed were evident in the renal papilla adjacent to the upper calyx.

Urinalysis showed a faint trace of albumin but only a rare pus cell. Examination of the urine was negative for tubercle bacilli.

The patient was again seen in April 1943. X-ray examination showed no significant change in the amount or character of the renal calcification. We have not seen the patient since that time.

DISCUSSION

In none of our cases have we obtained surgical or autopsy specimens of the kidney for histologic study. However, Govan[8] reports the necropsy examination of the case studied by Baines, Barclay and Cooke[9] wherein nephrocalcinosis was observed associated with hyperchloremia and low plasma bicarbonate in a woman 29 years of age. We are interested concerning the findings in the urinary tract:

Both kidneys were enlarged with dilated pelves and calyces which contained many light brown calculi of varying size. Some calyces contained single large stones and others innumerable small stones of similar color. Erosion and ulceration of the pelves were evident, with thinning of the renal parenchyma in addition to multiple stones in the right ureter.

Microscopically the glomeruli were enlarged, many having undergone hyaline obliteration, but there was no evidence of glomerulitis. The cells of the proximal tubules were exceptionally swollen and atypical due to the presence of large vacuoles. The nuclei were pushed to the base of the cells. Degenerative and regenerative changes were evident in the descending portion of the proximal convoluted tubule. Occasional calcification of necrotic cells was observed. Intense fibrosis made identification of the narrow portion of Henle's loop difficult but the ascending limbs were dilated, many containing casts which showed calcification.

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[8] Govan, A. D. T.: Quart. J. Med., 19: 277, 1950

[9] Baines, G. H., Barclay, J. A. and Cooke, W. T.: Quart. J. Med., 14: 113, 1945.

More significant changes were present in the collecting tubules. Occurrence of calcification was common both within the tubules and the necrotic epithelium. Calcified masses lay imbedded in surrounding fibrous tissue which appeared to have been extruded from the tubules. The ducts of Bellini also contained calcified material and many showed ulceration and severe inflammatory reaction which extended to the renal pelvis.

The findings in this case represent advanced disease. The patient was known to have had urinary calculi for at least 5 years and had experienced polyuria and thirst since the age of 10, which may have indicated the onset of her disease. However, except that the findings are more extreme, they agree with other reported pathologic studies in nephrocalcinosis[10] and consist of pronounced tubular changes with calcification in the distal and collecting tubules, as well as extratubular calcified concretions in the renal papilla.

We have now observed 12 cases of nephrocalcinosis in which a clinical diagnosis was made by means of roentgen examination of the kidneys. All but two of these patients have formed stones; in many instances the discovery of nephrocalcinosis was made only on consultation sought because of renal colic. As we reflect upon these cases, certain interesting points emerge: 1) I believe we are justified in assuming that the primary trouble is renal tubular damage brought on by some nephrotoxic agent, which may be bacterial or chemical. 2) The calcification follows this tissue damage and occurs chiefly in the distal and collecting tubules and extratubular tissue of the renal papilla. The term dystrophic calcification has been applied to this pathologic process long recognized by pathologists. 3) The tubular dysfunction may give rise to certain metabolic disturbances, notably hyperchloremic acidosis and disturbances in calcium and phosphorus metabolism. Rickets has been observed by Albright. 4) These tubular and papillary calcifications lead to the formation of urinary calculi. 5) As far as the radiologic findings are concerned, this is not always a diffuse bilateral disease; it may be unilateral or localized to only a small portion of the kidney. When one assembles all these facts, the mechanism for stone formation affords clinical support for the ideas propounded by Randall in 1936 and subsequently supported by Keyser.

As a result of clinical observation, extensive autopsy examinations and experimental studies, Randall came to the following conclusions:

1) "That in the absence of stasis, a primary renal calculus is dependent upon and arises because of a pathologic condition of the renal papilla.

2) "The pathologic condition is a varying degree of damage to the structures of the collecting tubules and supporting interstitial tissue.

3) "This damage is succeeded in the living by attempted repair in which calcium salts may be deposited.

4) "Such calcium salt deposition may be both intratubular and extratubular and of varying degree; in some slow, discrete and chronic; in others acute, rapid and overwhelming."

In his autopsy studies two types of lesions in the renal papilla were observed:

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[10] DAVIS, J. S., KLINGBERG, W. G. AND STOWELL, R. E.: J. Pediat., 36: 323, 1950.

Type 1, a calcium plaque predominantly interstitial and showing a slow, chronic course usually situated at the apex of the pyramid; type 2, an intratubular deposition of calcium indicating a more acute and rapidly developing process.

Type 1 is most frequently on the side wall of the papilla and remains harmless until brought to the surface by growth and pressure. Once exposed, it is bathed in urine and, acting as a foreign body, becomes the nidus upon which any urinary salt may crystallize. Thus Randall demonstrated calcium phosphate, calcium oxalate, and uric acid calculi with the same calcium core.

In type 2 the calcium salts were principally intratubular producing tubular damage. Only calcium phosphate was demonstrated in this type and any stone formation occurred at the papillary tip where the morbid process was most advanced. In 1,154 autopsies type 1 was found in 19 per cent, and type 2 in only 1.9 per cent; there were 65 examples of calculus growing adherent to the renal papilla.

Based upon this concept, one may presume that the cases of nephrocalcinosis herein reported represent extreme examples of type 2 lesion.

Randall emphasized the pathologic findings observed in the renal papilla. However the evidence presented by these cases of nephrocalcinosis justifies the concept that the pathologic process may begin even higher, certainly in the distal convoluted tubule and possibly in the proximal tubules.

Even in this group of cases demonstrable by roentgenogram the extent of the injury and resulting calcification are variable. Furthermore, cases of nephrocalcinosis are known to have existed in which the lesion was not demonstrated by x-ray. We may assume that it is possible to have minimal, limited and localized renal tubular damage which is followed by calcification. This small calcific fragment works its way down through the collecting tubules, perhaps as a foreign body, and finally emerges at the tip of the renal papilla. Then, as Randall comments, it becomes the nidus around which urinary salts accumulate to become a calculus, which finally drops off to be passed. This would explain the frequent clinical observation of the patient who passes a single stone and never has a recurrence. Conversely, recurrent stones may be due to more widespread kidney damage or to some constant source of repeated damage to the renal cells. Focal infection deserves consideration.

Perhaps we urologists have become accustomed to thinking of the renal pelvis and the minor calyces as the top of the urinary tract. The problems presented by the disease under discussion indicate that we must consider the collecting tubules and even the nephron in order to understand this and possibly other diseases as well. We have, in these cases, a clear demonstration of what is perhaps the chief mechanism of stone formation. That many of these cases are visible to radiographic demonstration is unfortunate for the patient as it bespeaks extensive renal damage with an uncertain or unfavorable prognosis. However it may serve us, for by analogy we may picture the same process in its minimal form not visible to x-ray until a sizable stone develops. As we learn the causes of renal tubular injury we may also learn the manner in which to prevent many of these primary renal calculi.

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ETIOLOGY AND PREVENTION OF RENAL CALCULI

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The investigation of the etiologic factors associated with the formation of renal calculi has been stressed by urologists and urologic surgeons interested in the experimental production and dissolution of renal calculi and the clinical aspects of renal lithiasis.

The detection and recognition of the causative factor or factors permit the establishment of a postoperative regimen instituted to minimize the incidence of recurrent stone formation.

In instances in which lesions exist which are amenable to correction by surgical intervention, it may be accomplished at the time the primary calculus is removed from the kidney.

It is generally conceded that no single causative factor is instrumental in the production of all renal calculi; thus in the period of preoperative investigation a comprehensive search is required to ascertain the etiologic factor in the individual patient.

In view of the high incidence of recurrence cited in the past, the surgical removal of the calculus from the kidney must be considered as but one phase in the management of the patient. During the period of preoperative investigation, the following contributing factors merit attention:

VITAMIN A DEFICIENCY

1. Numerous clinical and experimental observations demonstrate the relationship between calculus formation and the absence or a deficiency of certain essentials in the diet. This was especially stressed by Fujimaki[1] and McCarrison.[2] These observers noted "stone areas" or geographic areas in which calculi occurred with unusual frequency in India and China where the people subsist on improperly balanced diets. Since their report additional "stone areas" have been recognized in Turkey, Russia, Egypt, Palestine, England and France, and in other countries.

From the analysis of the diets in these localities, it is evident that the populations subsist on diets which are deficient in certain essentials, or foods poorly balanced in acid and alkaline ash. Several observers have stressed the deficiency of vitamin A in the diets of the peoples in these localities.

2. In the last century, calculus disease was one of childhood in England and France. Joly[3] believes that it is no longer considered a disease of childhood but rather one of adult life. This decrease in the incidence of stones in children has been attributed to nutritional and dietary progress. In contrast to this observa-

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Read at annual meeting. American Association of Genito-Urinary Surgeons, Skytop, Pa., May 17, 1951.

[1] Fujimaki, Y.: Japan M. World 6: 29, 1926.

[2] McCarrison, R.: Brit. M. J., 1: 1009, 1931; also Lancet 1: 1413, 1931.

[3] Joly, J. S.: Stone and Calculus Disease of the Urinary Organs. St. Louis: C. V. Mosby Co., 1931.

tion, in Russia 55 per cent of calculus disease occurs in children below the age of 15.

3. Geza Illyes[4] stated that the incidence of renal calculi increased enormously since World War I, especially in countries where the inhabitants subsisted on a deficient or poorly balanced diet for an extended period.

In the past we utilized the biophotometer test to determine varying degrees of vitamin A deficiency. It is my belief that this is not an adequate method of determining vitamin A deficiency; the results are not consistent and the antimony trichloride test is the preferable procedure.

In the experimental laboratory I have produced in the white rat: a) stones composed of phosphates with traces of carbonates; b) stones composed of carbonates with traces of phosphates; oxalate and oxamide calculi in rabbits, uric acid stones in the Dalmatian dog, ammonium magnesium phosphate stones in the dog, calculi composed of the acetyl salts of the sulfonamides in rabbits, and in one patient a cystine renal calculus which was dissolved by employing the alkaline ash diet.

Even if vitamin A deficiency is not demonstrable this diet should be administered postoperatively for its specific healing effect on epithelial structures.

The relationship between foci of infection and calculus formation is subject to question. Rosenow and Meisser[5] demonstrated the specificity of the streptococci in the production of urinary calculi. This work has not been confirmed in other experimental laboratories. They inoculated the pulp of dogs' teeth with streptococci isolated from the urine of patients with calculus disease. The dogs developed calculi and the streptococci were isolated from the urine. I believe foci of infection in the teeth, prostate and cervix should be eradicated.

INFECTION IN THE URINARY TRACT

The relationship between urinary tract infections and calculus formation is evident from a review of the literature. Bugbee[6] in a critical review of 29 patients with renal lithiasis elicited a history of a pre-existing pyelonephrosis in 23 instances.

In a review of 800 consecutive cases of renal lithiasis, I found the culture of the urine to be sterile in 13 per cent.

In 400 consecutive patients observed with recurrent renal calculi, in 288 cases of unilateral stones, the urine was sterile in 216 instances; in 112 cases of bilateral renal calculi the urine was found to be sterile in 20. These studies were made regardless of the size of the calculi.

Harrington[7] in a review of 480 cases of urolithiasis, noted that the culture of the urine was sterile in 26 per cent. Lett[8] in a study of 419 cases of urolithiasis observed that the culture of the urine was sterile in 18 per cent. Thus while renal infection is not a necessary precursor of stone formation, it is frequently observed.

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[4] Illyes, G.: Orvosi hetil, 78: 889, 1934.

[5] Rosenow, E. C. and Meisser, J. G.: Collect. Papers Mayo Clin. and Found., 13: 253, 1921.

[6] Bugbee, H. G.: Trans. Am. Assoc. Genito-Urin. Surg., 25: 121, 1932.

[7] Harrington, H. L.: J. Urol., 44: 507, 1940.

[8] Lett, H.: Brit. J. Urol., 8: 205, 1936; also Proc. Roy. Soc. Med., 29: 1357, 1936.

Complete bacteriologic study is essential including a gram stain of the urinary sediment, culture, test for urea-splitting properties of the offending organism and sensitivity tests.

STASIS

In certain instances renal stasis appears to precede calculus formation. Stasis is conducive to the shifting of the pH of the urine to the alkaline side, and produces a fertile field for bacterial growth.

The presence of stasis may be visualized by excretory urography and, when secured prior to operation, permits correction of the causative factor at the time of surgical intervention. Likewise an initial film and an excretory urogram should be secured before the patient is dismissed from the hospital to determine whether or not stasis has been eliminated and to avoid misrepresentation of false recurrences at a later date.

HYPERPARATHYROIDISM

The relationship between hyperparathyroidism and renal lithiasis has received considerable attention in recent years. In 1934 Barney and Mintz[9] reviewed a series of cases in which the diagnosis of hyperparathyroidism was confirmed by surgical intervention. In 61 per cent of this group calculi were demonstrable in the urinary tract. They stated that hyperparathyroidism is a causative factor in 4 to 5 per cent of the cases. They postulated further that in approximately 70 per cent of cases of hyperparathyroidism calculi are discernible, and in 38 per cent of patients there may be pathologic changes in the bones and urinary tract.

Sangree[10] in a review of 50 cases of renal and unilateral calculi observed one patient with a tumor of the parathyroid gland. Braasch[11] cited an incidence of 0.2 per cent, and I have observed a frequency of 1.8 per cent.

Recently Beard and Goodyear[12] in a review of 150 cases of renal lithiasis stated that hyperparathyroidism was present in 8 per cent of cases.

I believe that hyperparathyroidism is more frequently an etiologic factor than has been presumed in the past. An intensive study is essential to eliminate this possibility. The level of the serum calcium and serum phosphorus and total proteins cannot be evaluated by one determination, but should be repeated. If there is an elevation of the serum calcium and a lowering of the serum phosphorus additional studies are necessary. The patient is hospitalized and after following the Aub diet for 3 days, 24 hour studies are made of calcium excretion in the urine. A Sulkowitch test of the urine detects the gross presence or absence of hypercalcinuria, and roentgenologic survey may reveal bone lesions compatible with the diagnosis of hyperparathyroidism. Routinely, the calcium ion concentration should be determined as it is of primary physiologic and clinical importance. The calcium ion concentration is obviously a resultant of the equilibrium between the total calcium and the total protein. That the investigation of the blood calcium alone does not suffice is evidenced by the fact that fluctuation in the total calcium occurs in response to fluctuations in the concentration of the total proteins in the plasma. Such a fluctuation in the total calcium in the plasma, therefore, is essential in maintaining a normal calcium ion concentration. An increase in the calcium ion concentration in the plasma is strong evidence of hyperfunction of the parathyroid glands.

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[9] Barney, J. D. and Mintz, E. R.: J. A. M. A., **103**: 741, 1934.

[10] Sangree, H. K.: J. Urol., **59**: 842, 1948.

[11] Braasch, W. F. and Foulds, G. C.: J. Urol., **11**: 525, 1924.

[12] Beard, D. E. and Goodyear, W. E.: J. Urol., **64**: 638, 1950.

Hypercalcinuria does not necessarily imply the presence of hyperparathyroidism, as 40 to 60 per cent of patients with renal lithiasis may have hypercalcinuria in the absence of hyperactivity of the parathyroids. The excretion of calcium in the urine is influenced by varying the calcium and phosphorus content of the food, the intake of vitamin D, the renal function and the acidity of the ash in the diet.

CALCIUM PLAQUES

Randall[13] in 1937 described the calcium plaques involving the papilla and stated that they had been observed in the renal papilla in 140 of 609 cases in which postmortem studies were made. In this series of 49, renal papilla with adherent stones were observed.

Vermooten[14] in 1941 in a study of 1060 pairs of kidneys in South Africa stated that in only 88 pairs were calcium plaques observed. Kjolhede and Larsen[15] did not consider that Randall's papillary lesions were new pathologic entities.

Domanski[16] in the experimental production of calcium oxalate calculi in albino rats reproduced the papillary lesions and the calculi were either attached to the tip of the papilla or were loose in the renal pelvis. The incidence of stone formation was highest in the group of rats having a diminished intake of vitamin A.

NEPHROCALCINOSIS

The relationship between nephrocalcinosis and renal calculi is evident by the clinical observation that the first symptom of the disease may be an attack of colic with or without the passage of the calculus. In addition to the characteristic roentgenographic findings of clusters of calcific deposits in the renal pyramids, calculi may be observed in a calyx or the renal pelvis.

The disease was described by Butler, Wilson and Farber[17] in 1936. Since that time additional cases have been reported by Albright,[18] Engel[19] and others.

A diagnosis is established by the typical x-ray findings, acidosis, hyperchloremia, a negative calcium balance, and hypercalcinuria.

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[13] Randall, A.: Surg., Gynec. and Obst., **64**: 201, 1937.

[14] Vermooten, V.: J. A. M. A., **109**: 857, 1937.

[15] Kjolhede, K. T. and Larsen, H. K.: J. Urol., **47**: 45, 1942.

[16] Domanski, T. J.: Am. J. Clin. Path., **20**: 707, 1950.

[17] Butler, A. M., Wilson, J. L. and Farber, S.: J. Pediat., **8**: 489, 1936.

[18] Albright, F. and others: Bull. Johns Hopkins Hosp., **66**: 7, 1940.

[19] Engel, W. J.: J. A. M. A., **145**: 288, 1951.

It is Albright's theory that nephrocalcinosis is the result of damage and dysfunction chiefly of the distal convoluted tubules.

METABOLIC DISEASES

Various metabolic diseases may be associated with an excessive excretion of crystalloids in the urine. The following merit investigation:

Gout. Gout is a metabolic disease in which excessive amounts of crystalloids may be present in the urine. The patient may experience repeated attacks of colic due to the passage of a stone or showers of uric acid crystals. The presence of uric acid crystals may be detected in the urine. A normal person excretes 0.3 gm. to 1.2 gm. of uric acid daily; the amount is obviously influenced by diet. It is of interest to note that there may be an elevation of the blood uric acid, and uric acid calculi in the urinary tract, while the patient exhibits no clinical symptoms of gout.

Cystinuria. Cystinuria is a familial disease stated to be caused by the derangement of intermediate protein metabolism. Normally cystine is oxidized, and the sulfur is excreted as a sulfate. In cystinuric patients the cystine is not oxidized to sulfate and the metabolism of the cystine conversion to taurine is undisturbed. It is estimated that 2.5 per cent of patients with cystinuria develop calculi.

Seeger and Kearns[20] in 1925 collected 181 cases of cystinuria from the literature and in 124 instances calculus disease were noted.

The cystine may be found in the urine partly in solution, and also in crystalline deposit.

In instances in which a family history of calculus is elicited, the urine should be tested for cystine, and microscopic study for crystals is advisable.

Oxaluria. Approximately 12 to 30 mg. of oxalic acid, which has an exogenous and endogenous source, is excreted in the urine daily. Examination of the urine for crystals should be a routine procedure.

Davis, Klingberg and Stowell[21] cited a case of a boy 3 years of age with nephrocalcinosis, nephrolithiasis and calcium oxalate crystals in the kidneys and bones. They suggested this might be due to a defect in the calcium or oxalate metabolism in the patient.

Xanthinuria. In 1934 Kretschmer[22] collected from the literature a series of 15 xanthine calculi cases and added an additional one. We have observed 5 patients with xanthine renal calculi. Uric acid is the most important purine in the urine but 30 to 50 mg. of purine bases, xanthine, hypoxanthine, guanine and adenine are present also.

Phosphaturia. Phosphaturia may be of three types: 1) temporary phosphaturia, induced by partaking of foods with a high alkaline ash or medication; 2) permanent infected phosphaturia due to the presence of urea splitting organisms; 3) permanent noninfected phosphaturia, the cause of which is obscure.

Thus, it is evident that many factors may be associated with calculus formation. Unless a comprehensive investigation is pursued, and corrective measures instituted, the incidence of recurrent stone formation will remain relatively high. Elimination or correction of the causative factors will be accompanied by a reduction in the morbidity of this disease.

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[20] Seeger, S. J. and Kearns, W. M.: J. A. M. A., 85: 4, 1925.

[21] Davis, J. S., Klingberg, W. G. and Stowell, R. D.: J. Pediat., 36: 323, 1950.

[22] Kretschmer, H. L.: J. Urol., 38: 183, 1937.

Several procedures may be employed to minimize the incidence of recurrent calculus formation:

1) Maintenance of a large fluid intake (distilled water) and output for 1 year.
2) Elimination of foci of infection.
3) Eradication of infection in the urinary tract.
4) Correction of stasis.
5) Correction of metabolic diseases.
6) Exploration of parathyroid glands in the event that a diagnosis of hyperparathyroidism is established.
7) Additional vitamin A.
8) Chemical analysis of the calculus.
9) Dietary management.
10) Basaljel or estrogen therapy.
11) Treatment of nephrocalcinosis.
    a) Reduce the hyperchloremia.
    b) Correct the acidosis.
    c) Correct the negative calcium balance.

The dietary routine to be advocated is governed by the chemical constituents of the calculus, optical crystallographic or petrologic study, the pH of the urine from the kidney which harbored the calculus, the crystals observed in the urine, and the blood chemistry findings.

The purpose of the diet is to shift the pH of the urine to a point at which the crystalloids, which were constituents of the primary calculi, are maintained in complete solution.

Thus by maintaining the salts in complete solution, the precipitation and formation of accumulations of crystalloids are prevented, thereby eliminating a requisite essential for the formation of renal calculi. Scott has stated that, in most patients with urinary calculi, stone formation is limited to a specific type. When acid stones are formed, usually, an alkaline ash diet will not cause formation of alkaline stones, and vice versa.

In patients in whom the calculi were composed of phosphates, carbonates, or a combination of the two, the high vitamin A acid ash diet is recommended. By maintaining the pH of the urine between 5.2 and 5.4 the phosphates and carbonates are sustained in complete solution, thus eliminating from the urine crystals and sediments which precipitate in alkaline urine. I prefer to determine the pH of the urine in each individual case to ascertain the point at which the salts are maintained in complete solution, as some degree of variation may occur.

For uric acid, cystine and xanthine calculi, the high vitamin A, alkaline ash, low purine diet is advocated. The pH of the urine is shifted by modifying the constituents of the diet, to a point where these salts are not precipitated in the urine and, at the same time, the alkaline salts are maintained in complete solution. Foods with a high purine content are restricted to minimize the amount of uric acid and urates available to be precipitated in the urine.

When the stone is composed of oxalates, foods with a high oxalic acid content are restricted. The oxalates are precipitated in a wide range of urinary reaction; the pH of the urine may be acid or alkaline. To increase the solubility of the calcium salts, it is advisable to maintain the pH of the urine slightly on the acid side. It is obvious that various combinations of the diet may be required, and this is determined by the chemical constituents of the stone.

This same dietary routine is instituted in the group of patients for whom the diet is prescribed in an attempt to produce dissolution by dietary means. The diet is not applicable for the dissolution of oxalate calculi, inasmuch as oxalates precipitate in urine, the reaction of which is acid or alkaline.

I again reiterate that the role of the diet is only for those patients in whom the pH of the urine may be controlled by dietary means; this constitutes the majority.

It does not suffice to merely prescribe the diet; the patient is required to make daily pH determinations of the urine (which takes only a few moments) and present them to the physician at monthly intervals. In instances in which the pH of the urine is not maintained at the desired level, further dietary adjustment is essential.

There are instances in which the pH of the urine cannot be controlled by dietary means. Usually this occurs in the presence of a urea splitting infection in the urinary tract which cannot be eradicated by the various chemotherapeutic agents available at the present time. Under these conditions the calculi are usually phosphatic in type or composed of phosphates and carbonates.

The role of aluminum gel in this group cannot be overstressed. The principle involved in aluminum gel therapy rests on the fact that the aluminum gel in passing through the gastro-intestinal tract unites with the phosphorus to form insoluble aluminum phosphate which is excreted as such from the bowel. This minimizes the resorption of phosphates from the gastro-intestinal tract, reduces the serum phosphorus, and favors a more complete tubular resorption of phosphatic ions; thus a reduction in urinary phosphate excretion occurs. In reality the phosphates, instead of being excreted in the urine, are now being eliminated in the stool.

The extent of this reaction is determined by the intake of phosphorus and the type and dosage of the aluminum gel prescribed. A normal person, on an average diet, excretes approximately 1 gm. of urinary phosphorus daily. The dosage of the aluminum gel is determined by study of the urinary phosphorus excretion which can readily be reduced to 200–300 mg. per 24 hours.

One other type of therapy may prove to be of value but, while I have used this in experimental work, insufficient data are available to recommend it generally. This consists of the use of estrogens.

The rationale for the use of estrogenic hormones rests on the concept that citric acid in the urine is not a waste product but a useful constituent by virtue of its capacity to enhance the solubility of calcium, and also on the ability of estrogenic hormones to increase the excretion of citric acid and to reduce that of calcium. At the present time I have used this type of therapy only for those patients having had hysterectomies.

Thus the management of the patient with renal lithiasis is a complex problem of which surgery constitutes but one phase. The fields of chemistry, bacteriology, endocrinology, dietetics and others are involved. Failure to recognize and eradicate the etiologic factors will be followed by a high incidence of recurrent calculus formation. The efficacy of the dietary regimen is determined by the rigidity of its enforcement.

In conclusion, familiarity with all phases of calculus disease, close adherence to the known concepts of stone formation, and the utilization of procedures to minimize recurrent lithiasis, will be attended by a pronounced reduction in the morbidity of calculus disease.

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REVIEW OF ONE YEAR'S EXPERIENCE WITH THE JOHNSON EXTRACTOR IN THE MANAGEMENT OF URETERAL AND RENAL CALCULI

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Of all the instruments offered through the years for the cystoscopic delivery of ureteral stones[1] we have been most gratified by the use of the wire basket snare or dislodger devised by a former member of the Western Section, Dr. Franklin P. Johnson of Portland, whose untimely death occurred in 1943. In reviewing the origin of the instrument,[2] we were interested to recall that he first presented it formally in 1936 at the meeting of the Western Section in Salt Lake City, the city in which the work here reviewed was done. In 1935, Dr. Johnson had shown an experimental model at the meeting of the American Urological Association in San Francisco, and had demonstrated how easily he could withdraw a stone from a rubber tube with the instrument. At that time, however, he had not yet extracted a stone from the ureter.

When Johnson's "snare" became available we were already favorably impressed by the Councill dislodger, which was the first instrument to utilize the principle of the wire cage (fig. 1). This principle, we regard as a distinct advance in the manipulative treatment of ureteral calculi. It is based on the sound mechanical conception of enveloping the calculus in a mesh of smooth wires, under circumstances where traction narrows the girth of the basket and tightens its grip upon the stone. The Johnson basket seems to us to be a refinement of the Councill instrument. It is smaller, less rigid, and therefore safer. Like the Councill basket it provides the stone with a wedge-like presenting point and a "skid" to facilitate its extraction. The elimination of the pull wire in the Johnson instrument has made it more flexible without impairing its success.

We believe that textbooks in urology tend to overpraise the multiple catheter technique for the extraction of ureteral stones, and we have never had much success with Howard's spiral dislodger. Since 1937, however, we have become increasingly dependent on the Johnson extractor, so that we now use it almost to the exclusion of other methods except open surgery. Our enthusiasm for it continues to grow and we are convinced that with it most stones in the lower third of the ureter can be delivered expeditiously and safely (figs. 2 and 3). Exceptions are those with extreme impaction or spasm, where no catheter or bougie will pass the stone, and those occasional giant calculi in the ureter too large to enter the basket and obviously suitable only for operation (figs. 4 and 5).

We judge from the literature that some urologists are deterred from the frequent

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 27, 1951.

The opinions are those of the authors and do not necessarily represent the policy of the Veterans' Administration.

[1] Alyea, E. P.: J. Urol. 40: 85–100, 1938.

[2] Johnson, F. P.: J. Urol., 37: 84–89, 1937.

use of such a device by fear of ureteral perforation. Any experienced cystoscopist will admit the need for caution in passing this instrument into an obstructed ureter, but the statistics on ureteral perforation are not unfavorable to its use. In 1946, Howard[3] reported 8 instrumental perforations of the ureter, all with catheters and bougies, and not one due to the use of a wire basket stone extractor.

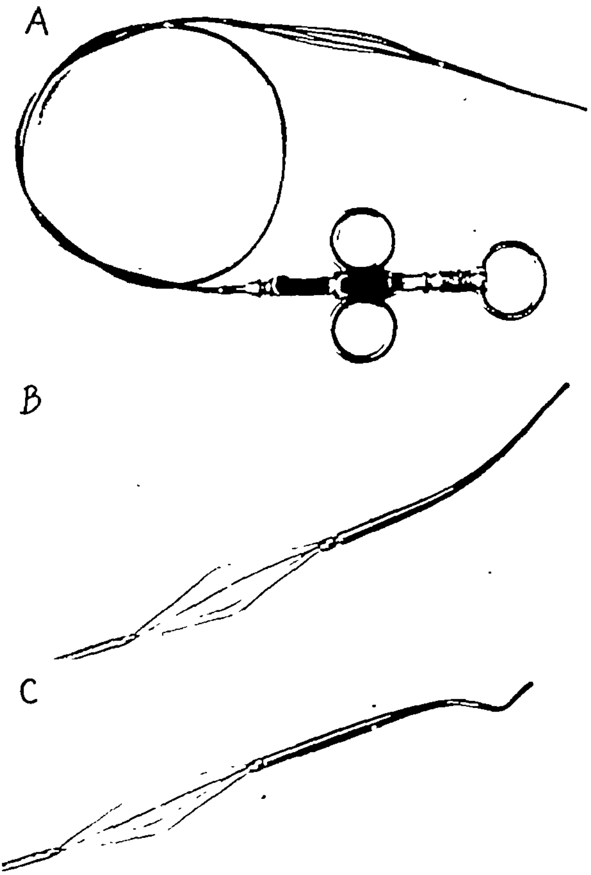

FIG. 1. *A*, Councill stone extractor, first instrument to utilize principle of wire cage. *B*, Johnson extractor. *C*, same, with recently available spiral tip.

We use the Johnson basket for some stones in the middle and upper third of the ureter, and to our great gratification one of us (E. Grua) recently caught a stone in the renal pelvis and withdrew it safely at a single manipulation. This we considered somewhat of a therapeutic triumph, for open surgery in this case would have been attended with great difficulty and damage to the kidney. It not only had an intrarenal pelvis, but the kidney was enclosed in dense adhesions from three previous operations for stone. This experience is similar to one reported by Ellik[4] in which a stone was extracted from the renal pelvis with a looped catheter. It need scarcely be said that we do not routinely recommend the attempt at cystoscopic delivery of stones from the pelvis of the kidney. Failure of the stone to engage in the upper ureter may be strong presumptive

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[3] Howard, F. S.: J. Urol., 56: 319–331, 1946.
[4] Ellik, M.: J. Urol., 56: 46–48, 1946.

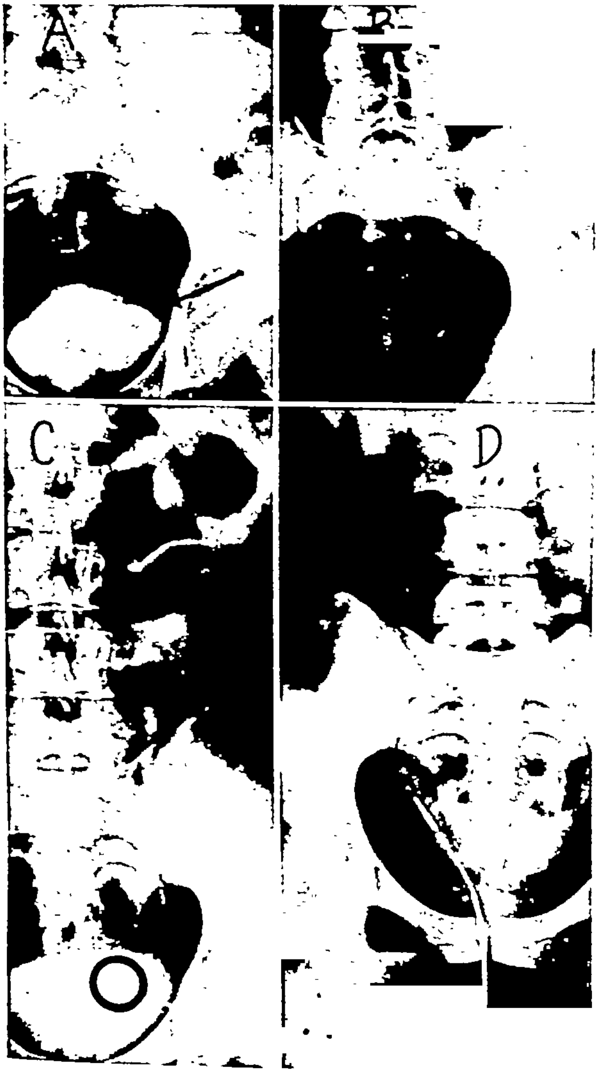

FIG. 2. *A*, *B*, typical examples of low ureteral stones removed with Johnson dislodger. *C*, stone impacted in intramural portion showing characteristic ureteral tortuosity from violent peristalsis. *D*, stone caught in wire basket. Flexible tip of dislodger is nonopaque to x-rays.

evidence of the same disproportion that makes obstetricians look with horror upon the application of forceps to the floating head.

Having heard the interesting discussion of the relation of chronic prostatitis to urinary calculi by Winsbury-White[5] in his Guiteras Lecture at the meeting

[5] Winsbury-White, H. P.: J. Urol. 36: 469-505 1936.

of the American Urological Association in 1936, we have been impressed by the almost universal increase in the leukocyte count in the prostatic fluid of the male patients we have treated for ureteral calculi. Moreover, minor degrees of reduction of the caliber of the penile urethra, congenital or acquired, also seem common in men with ureteral stones. Our manipulations are routinely done through the 24F Brown-Buerger cystoscope, and preliminary dilatation of the urethra with sounds seems much more often necessary before manipulation for stones than before routine cystoscopy. Thus we have come to suspect that two

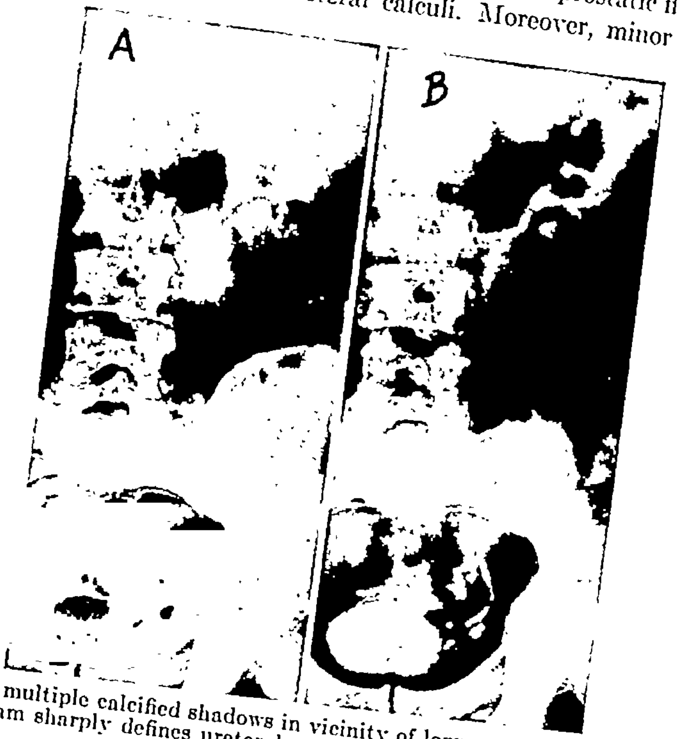

Fig. 3. *A*, *B*, multiple calcified shadows in vicinity of lower end of left ureter. Delayed excretory urogram sharply defines ureteral stone. It was quickly removed with Johnson snare.

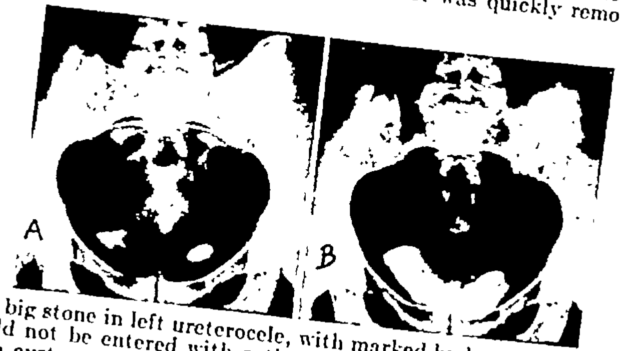

Fig. 4. *A*, *B*, big stone in left ureterocele, with marked hydro-ureter. Pinpoint orifice of ureterocele could not be entered with catheter. Face of ureterocele was extensively fulgurated through cystoscope, in hope that calculus would slough into bladder and be obtained by lithotrity. Several days later, patient passed stone.

factors predisposing toward calculi in the male upper urinary tract are chronic, often unsuspected, genital infections and minor degrees or urinary stasis from large caliber urethral stricture or latent prostatism.

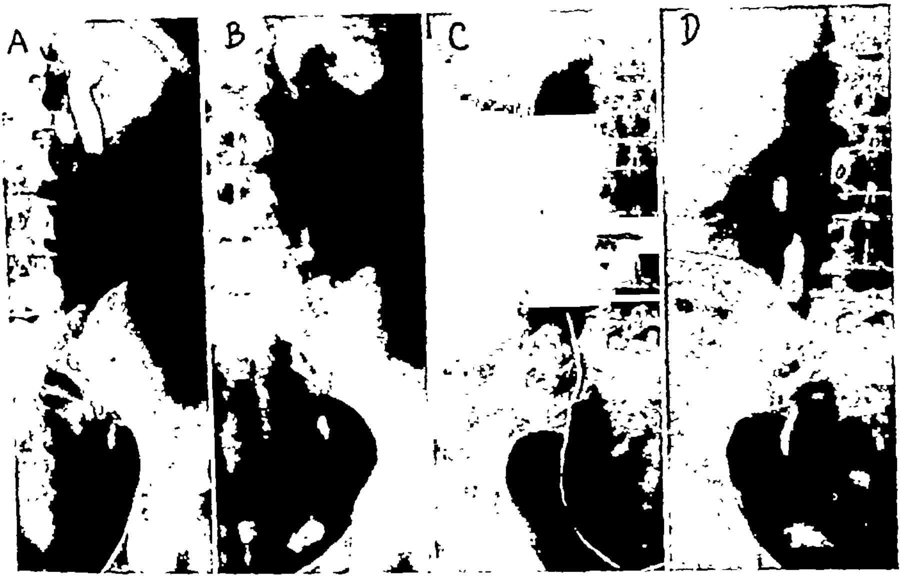

FIG. 5. *A*, large bizarre "icicle" calculi in left upper and lower ureter. Lower calculus was rejected for cystoscopic manipulation because of its great length. *B*, large calculus in left lower ureter treated by open surgery because of its size and presumable inflammatory infiltration of ureter (long duration of symptoms). *C*, *D*, big calculus in upper right ureter, causing total reflux of pyelographic medium. Because of size and tight impaction, this stone was also considered not suitable for endoscopic manipulation. Removed by ureterotomy.

TABLE 1. *Results of cystoscopic manipulation of ureteral calculi in 1950*

Number of patients	70
Extracted at first manipulation	43
Extracted at second attempt	4
Third or later attempt	2
Stone fragmented	3
Stone passed after manipulation	7
No follow-up	9
Resorted to open surgery	2
Position of the stones in the upper urinary tract	
Kidney	1
Upper half of ureter	6
Lower half of ureter	63
Complications of extraction	
Epididymitis	2
Perforation of the ureter	0
Deaths	0

We have recorded the results of manipulations for ureteral and renal calculi during the past year (1950). Most of the patients were seen in private practice, but 16 of them were treated by one of us (E. Grua) during the same period at the Veterans' Hospital in Salt Lake City. Table 1 gives our results.

Many of these manipulations for stone were carried out as office procedures, and some were sandwiched into the afternoon's work as emergencies within a few hours of the onset of the acute renal colic. We are convinced that prompt and efficient office treatment of such patients often is better than hospitalization. The patient is promptly relieved of his pain and has his stone in his hand, where it is no longer a menace to his kidney, while the hospitalized patient is usually tided through a wretched night with opiates in order to be cystoscoped during the regular surgical schedule the next day.

Some of our hospital manipulations have been done under spinal anesthesia with a small low injection of some short acting agent such as procaine (fig. 6). Most of the procedures, however, including all those done in the office, were accomplished with light pentothal sodium anesthesia, which we have found eminently satisfactory. The subject is somewhat controversial, but we believe that pentothal can be safely used in the office if the personnel is adequately trained. We have had no complications from its use in the last 10 years. We give no premedication and insist that the anesthesia shall be extremely light, limiting the total dose to ½ gm., and never injecting more of the drug after the patient has ceased to be able to count. The occasional mild protestations of a semiconscious patient are no hindrance to our work, and the patient, on awakening, rarely remembers any pain.

As a rule, the diagnosis of ureteral stone is made by the plain abdominal x-ray or excretory urogram, and the stone manipulation is the first cystoscopy. We begin by exploring the site of ureteral obstruction with a catheter or bougie. We prefer to use for this purpose an 8F Braasch bulb which frequently, due to its superior thrust, will find its way past an impacted stone to the renal pelvis when the ureter seems totally blocked to a smaller and more delicate catheter. A 6F spiral or olivary tipped ureteral catheter sometimes serves well as a preliminary to the Johnson extractor. We do not employ wire stylets to stiffen the catheter and do not inject oil or relaxing agents into the ureter. If the obstruction can be passed at all, we usually meet success with the introduction of the basket and can anticipate being able to present the stone to the patient within a few minutes. The extractor is inserted into the ureter well beyond the level of the stone and withdrawn with a gentle motion or rotation. The twisting must always be clockwise to prevent unscrewing the filiform tip. If the stone is not caught in one or two sweeps of the ureter it is not likely to be engaged at all.

The sensation of a stone caught in the basket is easily discernible, especially when the intramural portion of the ureter is reached. It is much like that of a "bite" to the fisherman. Resistance at the intramural portion of the ureter is overcome by firm but gentle traction, not unlike that used with obstetrical forceps. With big or jagged stones we believe the enveloping taped wires of the Johnson instrument make the traction much safer than with the looped catheter. Very rarely we have sent patients with firmly impacted stones in the basket to the hospital for light mechanical traction. Once the basket with the stone has been drawn into the bladder the cystoscope and extractor are removed as one. The stone usually remains in the basket, but if it is lost in the bladder it can

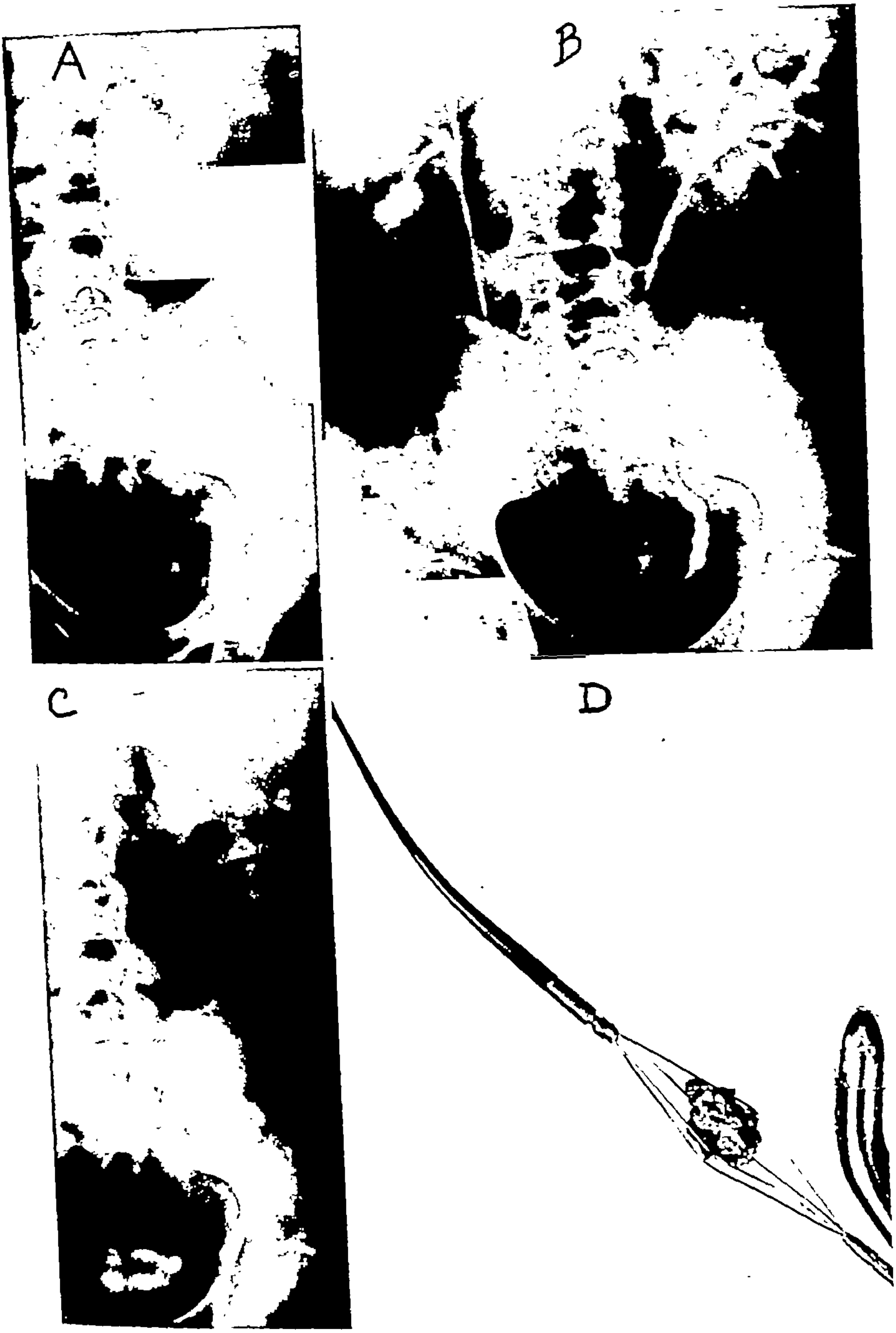

FIG. 6. *A*, large calculus in left lower ureter. *B*, retrograde pyelograms showing some dilatation of ureter just above stone, but not much effect on kidney. *C*, excretory urograms made 18 months later. Position of stone and its size are unchanged, but hydronephrosis has developed. *D*, stone in Johnson basket after its removal by 15 minutes of traction under low spinal anesthesia.

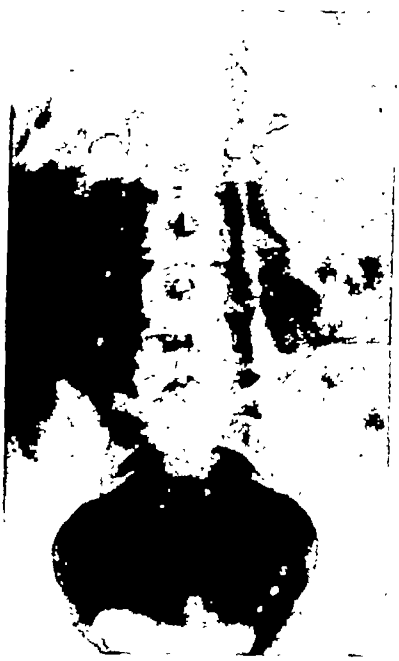

FIG. 9. Case 2. Tandem stones in left lower ureter, both removed in one sweep with Johnson basket. Office procedure under light pentothal anesthesia.

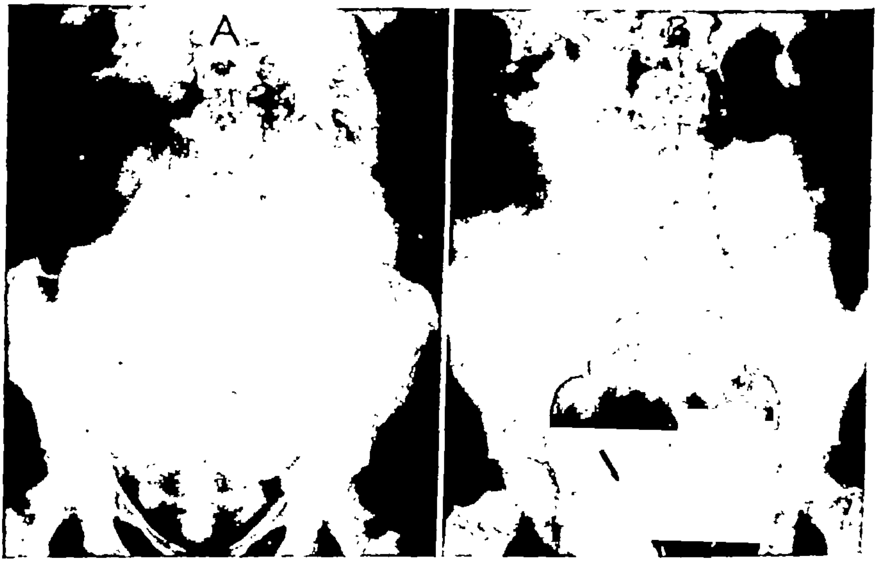

FIG. 10. Case 3. *A*, excretory urogram showing stone 1 cm. in diameter causing almost total obstruction of right lower ureter in woman 5 months pregnant. *B*, calculus engaged in Johnson basket with inlying catheter for vesical drainage. Following extraction of stone, pregnancy went to term, with normal delivery.

severe right abdominal pain of 24 hours' duration. Excretory urography revealed the right renal silhouette about 50 per cent larger than the left. Excretion on the right side was markedly delayed and, after 1 hour, large, faintly visible blobs indicated marked dilatation of the calyces. At the level of the right ischial spine there was a triangular calcified shadow about 1 cm in diameter (fig. 10).

Two days later, under pentothal anesthesia, the Johnson extractor was passed beyond the point of obstruction in the lower right ureter. Attempts to withdraw the instrument were unsuccessful and an x-ray showed that the stone was engaged in the basket. Accordingly it was left in place with an 18F Foley catheter in the bladder for drainage. Forty-eight hours later pentothal was given again and steady traction applied to the extractor. It came away and the stone was found in the wire basket. There were no complications and the patient was discharged in good condition with her pregnancy uninterrupted.

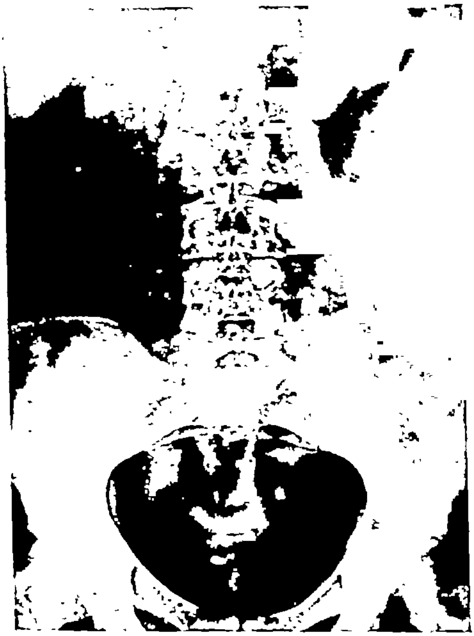

FIG. 11. Case 4. Stone in lower end of right ureter, and larger calculus causing total obstruction of left upper ureter. Stone easily removed from right ureter at office with Johnson extractor. Several days later, patient hospitalized, and other stone subjected to open surgery.

Case 4: Mrs. F. W. M., aged 56, had recurring pains in the abdomen and both loins for several months, accompanied by nausea and vomiting. Excretory urograms revealed a large impacted stone in the upper portion of the left ureter, with advanced hydronephrosis, and also a smaller stone in the lower end of the right ureter without much dilatation above it (fig. 11). Cystoscopy was done under pentothal in the office. The right ureteral orifice could be seen bulging, but the stone itself was not in view. It was disimpacted by pushing it back with a bougie and was then easily caught and delivered with the Johnson instrument. Several days later the patient was hospitalized and the large stone in the upper left ureter was removed surgically.

Case 5: Mrs. O. J. was not seen during 1950, so her case is not included in our statistics. It is presented to illustrate a simple method of disimpacting a stone in the lower end of the ureter in a female patient. She was in acute distress with a stone so tightly lodged in the intramural portion of the left ureter that no bougie would pass the obstruction. The stone was, however, easily palpable in the vault of the vagina, and we found it possible to stroke it upward with the finger tip, and then to introduce a cystoscope immediately and extract it from the ureter with the Johnson basket.

CONCLUSIONS

The Johnson wire basket "snare" or stone dislodger is a refined, efficient, mechanically correct device for the extraction of stones from the ureter. With it stones of suitable size, which are not hopelessly impacted, can usually be removed from the lower third of the ureter. With caution it can be used occasionally in the middle or upper third of the ureter, and we have even extracted one stone from the renal pelvis. So far as we know we have never perforated a ureter with the Johnson basket. In our hands it has come to be used almost to the exclusion of all other methods for the cystoscopic extraction of ureteral calculi.

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PRIMARY AMYLOIDOSIS OF THE RENAL PELVIS AND URETER: REPORT OF CASE

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Primary amyloidosis of the genito-urinary tract is a rare disease. In the majority of cases (8 cases)[1] the disease has been found in the bladder. The urethra and seminal vesicles have been involved.[2] Akimoto[3] was the first to describe a a focal nodule of amyloid in the renal pelvis. Lehmann[4] reported the necropsy findings of a localized amyloid deposit in the wall of the ureter. Our case of primary amyloidosis of the renal pelvis and ureter is the first to be reported in the English literature.

Amyloidosis has been classified by Dahlin as follows:

- I. Primary amyloidosis
  - A. Systemic
  - B. Focal or tumefactive
- II. Amyloidosis complicating myeloma
  - A. Systemic
  - B. Focal or tumefactive
- III. Secondary amyloidosis.

Primary amyloidosis of the genito-urinary tract is focal or tumefactive (I, B). Focal deposits of amyloid are seen in patients who usually have none of the diseases that commonly lead to secondary amyloidosis.

Amyloid is a homogeneous, amorphous, moderately eosinophilic material which shows metachromatic staining with methyl violet and methyl green. It usually has an affinity for Congo red and stains yellow or faintly pink with van Gieson's connective tissue stain.[5]

Amyloid is composed chiefly of protein-like materials and amino acids. The most favored theory on the pathogenesis of amyloid degeneration in tissues is one that considers it to represent an obscure derangement of protein metabolism.[5]

REPORT OF CASE

A 52-year-old white woman entered the Mayo Clinic on September 12, 1950, complaining of severe intermittent pain in the left flank of 2 weeks' duration.

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[1] Senger, F. L., Thomley, M. W. and McManus, R. G.: Primary amyloidosis of the bladder. J. Urol., **63:** 790-793, 1950.

[2] Craig, L. G.: Amyloid tumor of the bladder. J. Urol., **61:** 365-370, 1949.

[3] Akimoto, K.: Über amyloidartige Eiweissniederschläge im Nierenbecken. Beitz. z. path. Anat. u. z. allg. Path., **78:** 239-242, 1927.

[4] Lehmann, G.: Ueber örtliche Amyloidablagerung (lokales Amyloid) in der Wand des Harnleiters. Zentralbl. f. allg. Path. u. path. Anat., **68:** 209-213, 1937.

[5] Dahlin, D. C.: Classification and general aspects of amyloidosis. M. Clin. North Amer., **34:** 1107-1118, 1950.

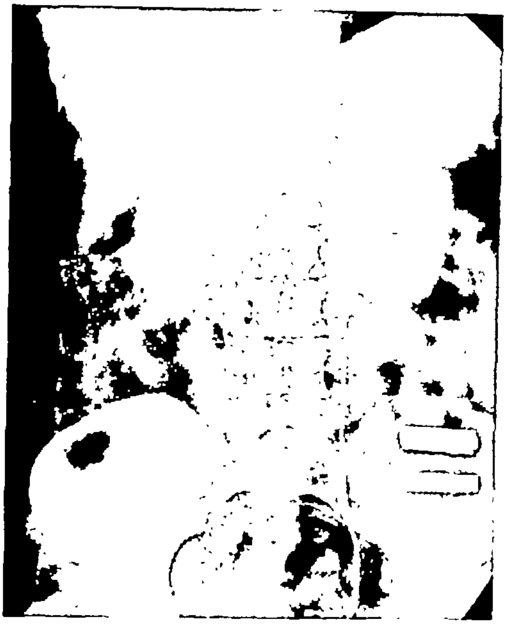

FIG. 1. Pyelogram in case of primary amyloidosis of renal pelvis and ureter.

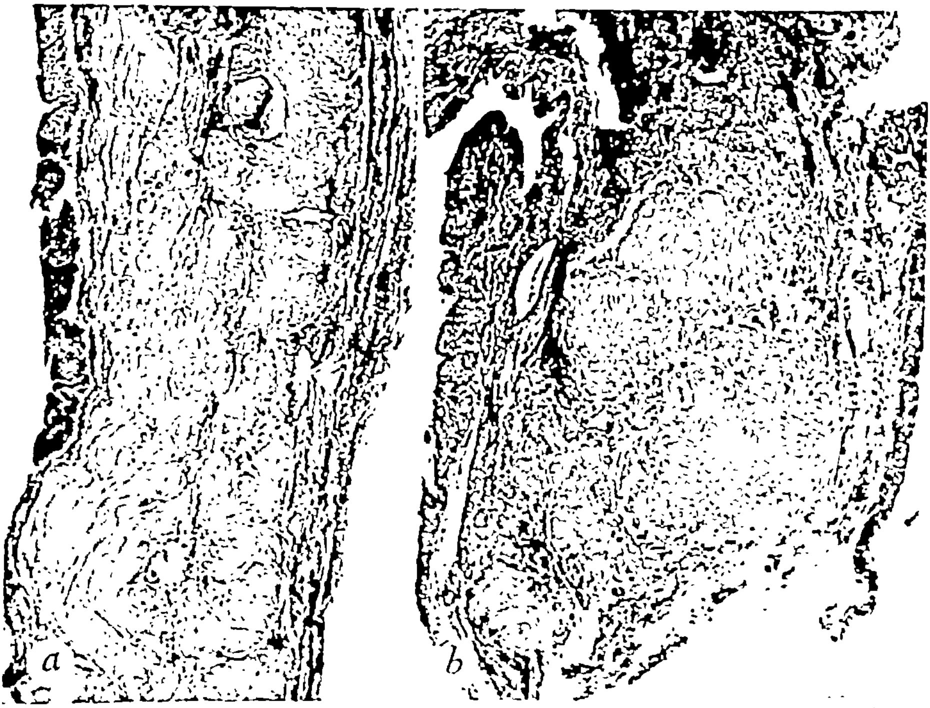

FIG. 2. Primary amyloidosis of renal pelvis and ureter. *a*, Homogeneous, amorphous material has replaced the muscle of the upper part of the ureter (hematoxylin and eosin × 70). *b*, Amyloid deposition in renal pelvis apparently confined to submucosal tissue (hematoxylin and eosin × 70).

Hypodermic injections were required for relief of pain. No associated urinary complaints were present. Thirteen years previously she had had severe pain in the left flank that lasted for about 1 week and that had not recurred until the present illness. No history of chronic illness was obtained. An excretory urogram and the results of urinalysis done here in 1947 were normal.

Physical examination revealed a slightly obese woman who appeared in good health and in no distress. The blood pressure was 130 mm. of mercury systolic and 70 diastolic. The heart and lungs were normal No masses were palpated in the abdomen. No tenderness was present in the flank.

Laboratory examination of the urine revealed a specific gravity of 1.020, absence of sugar and albumin, and an occasional pus cell. The hemoglobin content of the blood was 11.6 gm. per 100 cc; the leukocytes numbered 4,500 per cubic millimeter of blood. The concentration of urea was 20 mg. per 100 cc of blood. The Paunz test (Congo red) done postoperatively gave negative results.

An excretory urogram showed a left hydronephrosis (2+, graded on a basis of 1 to 4) with marked reduction in function. The source of obstruction was not apparent. The right kidney was not visualized satisfactorily for accurate interpretation. Cystoscopic examination showed a mild granular urethritis. A right retrograde pyelogram was normal. A ureteral catheter passed up the left ureter met an impassable obstruction 16 cm. from the meatus. An attempt to make a retrograde pyelogram on the left showed no evidence of dye above the third lumbar transverse process on that side. However, there was a definite outline of the pelvis and calyces, which were dilated (2+), as a result of the excretory dye given 24 hours previously (fig. 1).

Surgical exploration of the kidney and ureter was done on September 16, 1950, with the tentative diagnosis of a lesion of the upper part of the ureter, or a calculus of the pelvis that was not dense. No apparent cause for the obstruction was noted at operation. Nephrectomy was done and 6 cm. of ureter was removed.

Grossly the lower calyx and inferior portion of the pelvis and approximately 3 cm. of the ureter, as observed in the surgical specimen, had a waxy appearance. The upper calyx and superior portion of the pelvis appeared normal. Microscopically the muscle of the upper part of the ureter was replaced by a homogeneous amorphous material that stained pink with hematoxylin and eosin (fig. 2, *a*), reddish purple with methyl violet, purple with methyl green, yellow with van Gieson's connective tissue stain, and red with Congo red. There was amyloid deposition in the renal pelvis that was apparently confined to the submucosal tissue (fig. 2, *b*). The renal parenchyma was not involved with amyloid deposition.

This case presents another cause of hydronephrosis. Radiographically, the disease simulated a tumor of the upper part of the ureter. The mechanism of the hydronephrosis can probably best be explained on the basis of an actual encroachment on the lumen of the ureter by amyloid deposition and the replacement of the muscle of the ureter with amyloid. Thus the peristalsis of the ureter was diminished and the flow of urine impeded.

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TRIPLICATION OF THE URETER AND RENAL PELVIS

RICHARD D. GILL

Unusual anomalies of the genito-urinary tract occur fairly frequently compared with the other systems of human anatomy. The average urologic diagnostician manifests much more interest in the unusual anomaly and is much more apt to record his observations. Such was the case when we encountered a patient with three kidney pelves and three ureters on one side and two kidney pelves and two ureters on the opposite side.

EMBRYOLOGY

To understand the occurrence of ureteral anomolies one must be somewhat conversant with the fundamentals of the development of the genito-urinary tract. The metanephros frequently referred to as the permanent kidney makes its appearance in the human embryo about the fourth week. The metanephros may be divided into two portions, the secretory and the efferent apparatus. The efferent apparatus actually develops from the primary excretory duct, which by an outgrowth forms a ureter on either side. The ureteric anlage appears, according to Keibel and Mall, between the stages of 4.5 mm. and 5.3 mm. total length. The short ureteral bud grows at first almost altogether dorsally toward the vertebral column and the blood vessels lying in front of it, but later in embryos of 8.5 to 9.5 mm. it forms a curve, which becomes flatter with advancing age and the ureter grows cranially. The end of the bud becomes dilated, forming a cap, the beginning of the renal pelvis. The cap divides into a cephalic and caudal branch, each giving rise to smaller evaginations which are destined to become the calyces and the collecting tubules which eventually unite with the uniniferous tubules, these having been derived from the nephrogenic cord (renal blastema) or the true secretory anlage, the metanephros. The rectum, bladder, urethra, and the urogenital sinus are formed from a triple division of the cloaca. The lower portion of the excretory duct enlarges and becomes continuous with the adjoining portion of the cloaca. The ureteral bud is incorporated into that portion of the cloaca which is to become the bladder. About the fifth or sixth week the cloaca separates into a dorsal rectal and a ventral urogenital segment. Thus the ureter and wolffian duct come to empty into the vesico-urethral anlage, but acquire separate openings, the former emptying above and laterally into the future trigonum vesicae. From the wolffian duct is formed the posterior urethra, vas deferens, epididymis and the seminal vesicle.

Particularly pertinent to the understanding of the anomaly under discussion here, is the fact that there may arise two or three ureteral buds from the primary excretory duct or there may be a precocious splitting of a single ureteral bud, ureter fissus. This clefting may extend all the way down to its entrance into the bladder, thus giving rise to the cleft ureter with but a single orifice in the bladder. In instances of two or three or even multiple ureteral buds developing from the

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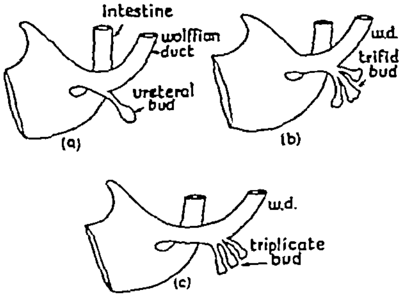
Read at annual meeting of Mid-Atlantic Section, American Urological Association, April 12, 1951.

primary excretory ducts the most caudal one usually shows the strongest development and reaches a more cranial level. This accounts for the fact that the lowest ureteral orifice on the trigone in case of multiple orifices connects with the upper most pelvis. This is referred to as the inversion relation of the ureteral orifices and their corresponding pelves. A mishap at this stage of development readily explains the congenital misplacement of some ureteral orifices, that is extravesical orifices or ureteral ectopia. There are those who disagree with this theory and think that multiple ureteral buds do not develop, that clefting occurs in a single ureteral bud and the result obtained depends only on the degree of clefting. Probably one embryologic theory will not explain all cases. From this extremely brief review or summary of the embryology involved it is not difficult to understand the manner in which triplication of the ureter might possibly occur. See figure 1.



Diagrammatic attempt to show development of-
(a) Normal ureter (b) Trifid ureter (c) Triplicate ureter

FIG. 1

Multibranched Ureters - 3 Cases

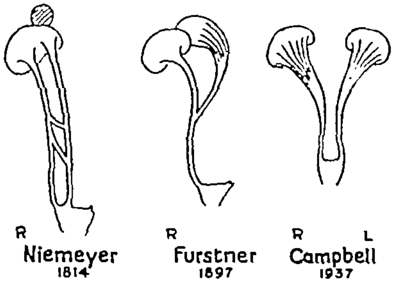


FIG. 2

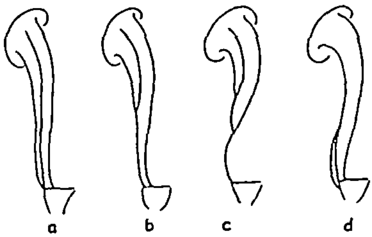
CLASSIFICATION AND INCIDENCE

Ureteral anomalies may be classified as 1) anomalies of number; 2) anomalies of origin and termination; and 3) anomalies of form, caliber, and structure. As to the first classification, there may be *A*, agenesis of the ureter, *B*, duplication of the ureter, *C*, triplication of the ureter, *D*, multi-branched ureters (fig. 2). In this discussion we are dealing only with triplication of the ureter.

Smith and Orkin in a statistical study of 471 congenital anomalies of the kidneys and ureters occurring in 18,460 consecutive urological admissions found no case of triplicate ureter. Campbell studying the uropathology in 26,480 autopsies found no instance of this anomaly. Abeshouse, in a most excellent discussion of ureteral ectopia and review of nearly 300 cases, found many concomitant anomalies of the genito-urinary tract but not one of ureteral triplication. While duplication of the ureter and kidney pelvis is relatively quite frequent, occurring in approximately 0.5 per cent of autopsy material and hundreds of cases being reported clinically, triplication of the ureter is undoubtedly one of the rarest anomalies of the upper urinary tract.

Lau and Henline in 1931 gave us one of our earliest discussions on this subject and reported a case of triplication of the ureter and also reviewed the literature. They found 7 cases reported in the world literature from postmortem examinations, but there were insufficient data to authentically classify these cases. Miller, in 1938, reported a proven case of triplication of the ureter. Burt, Lane, and Hamilton reported a case in 1941, and incidentally in their case one of the three ureters was ectopic. Woodruff, also, in 1941 reported a case. MacLean and Harding reported a case in 1945. Irvine Smith, in 1946, reviewed the world literature and gave a very excellent report on this subject and added a case of his own. He classified the triplicate ureter into the following types (fig. 3): 1) *triple ureter*, in which there are three separate and distinct ureters opening into the bladder or elsewhere; 2) *double ureter with one bifid*, in which two ureters may unite, leaving only two orifices (fig. 4); 3) *trifid ureter*, in which all three ureters may unite and drain through a single orifice (fig. 5) and 4) *double, with inversion Y bifurcation* and resulting three orifices.

Types of triplicate ureter



(a) Triple (b) Double with one bifid (c) Trifid
(d) Double with inversion Y bifurcation

Triple Ureter 4 cases

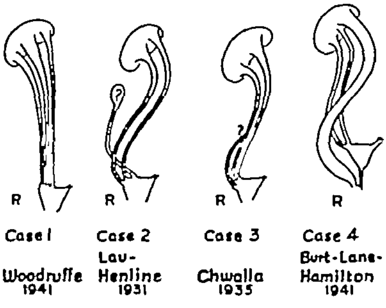


FIG. 3

Smith, in his exhaustive review of the literature in 1946, was able to find *four* cases of triple ureter, *two* cases of double ureter with one bifid and *four* cases of trifid ureter and added one of his own making five or a total of eleven cases of ureteral triplication.

We have been able to find one additional case, that reported by Withycombe in 1950 which is classified as a trifid ureter. The case herein reported is classified as a trifid ureter also and therefore brings this group to seven reported cases, and all cases of triplication of the ureter to thirteen. There is no doubt that there have been a fair number of unreported cases. The average text in urology does not mention the possibility of this anomaly. However, in Campbell's *Pediatric Urology* there is a picture of a trifid pelvis in a horseshoe kidney. In Wesson's *Urologic Roentgenology* there is a photograph, courtesy of A. K. Merchant, of triple renal pelves and ureters. In an article by Braasch and Scholl in 1922, on duplication of the renal pelvis and ureter, there is a photograph of three separate pelves leading from a common ureter. These have apparently been overlooked in the various surveys of the literature. In spite of the undoubted possibility of a number of unofficially reported cases, the fact still remains that triplication of the ureter is extraordinarily rare.

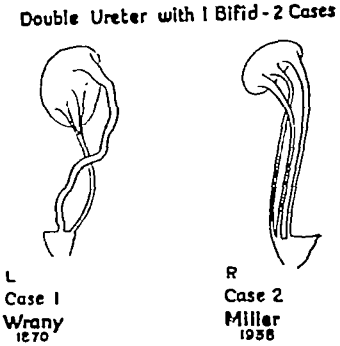


FIG. 4

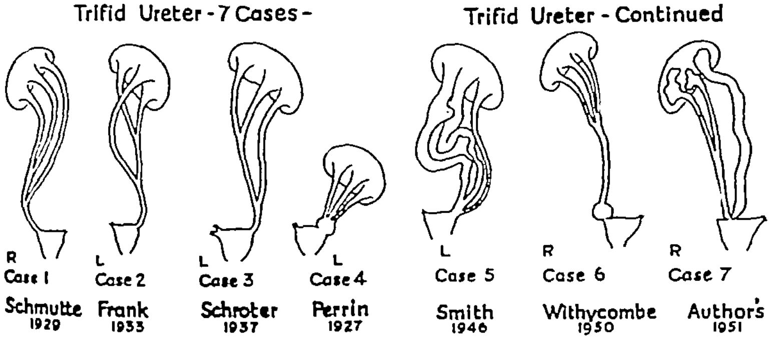


FIG. 5

SIGNS AND SYMPTOMS

There are no pathognomonic signs or symptoms of this condition; the diagnosis is made by urography, at operation or at autopsy.

CASE REPORT

Mrs. M. Y., a white married woman, 31 years of age, was referred to one of our general surgical colleagues with a working diagnosis of subacute appendicitis. The patient revealed that she had had some moderate attacks of pain in the right lower quadrant for several months. The present attack during the previous 48 hours had been much more severe and had required two hypodermics for relief. There had been no pain in the right kidney region posteriorly and no radiation of the pain to the genitalia or bladder region. There had been no dysuria or hematuria, and no chills or high fever. The patient's past genito-urinary history was entirely negative. There had been no attacks of any febrile condition in childhood that might have been interpreted as pyelitis. She was the mother of three children and had had no genito-urinary complications during pregnancy. On admission to the hospital patient's temperature was 99.6F. Routine blood work and blood chemistry showed no abnormalities except a leukocytosis of 13,000.

Physical examination was negative except for the right abdomen, where there was well marked tenderness over McBurney's point, but no muscle spams, and there appeared to be a rather large indefinite mass, moderately tender, extending upward into the right upper quadrant and into the right flank. The mass was soft and extremely hard to outline and appeared to move somewhat with respiration. The catheterized bladder urine was persistently alkaline and loaded with pus and the patient was referred to us for complete urological study.

At cystoscopy the bladder showed a chronic inflammatory reaction throughout with much purulent debris over the bladder floor. On the left side of the trigone there were two ureteral orifices. On the right side there was one orifice which was slightly larger than normal, and it was noted that the efflux of urine from the right orifice was more frequent than usual and the orifice seemed to gape open in a rather peculiar manner. Some obstruction was met about three inches above the bladder to the passage of a ureteral catheter on the right side. No obstruction was met to the passage of catheter in either of the two orifices on the left side. Retrograde pyelographic pictures demonstrated that we were dealing with an unusual anomaly, the exact nature of which would require further study, plus an impacted, rather large, ureteral calculus on the right side (fig. 6, A). There were two large atypical renal pelves with two hydro-ureters which apparently united above the impacted stone. There obviously was marked destruction of renal parenchyma and marked decrease in function on the right. Culture of the urine showed B. coli and bacillus alcaligenes. Function on the left side was normal. Shortly after the original urological study, the patient had severe chills and fever with an acute exacerbation of pain in the right flank and right kidney region posteriorly and an increase in the size of the mass in the right abdomen. In fact, she became sicker than she had ever been in her life. Attempt was made to introduce a ureteral catheter up the ureter past the stone for drainage of the acute process. This, however, met with failure. It was believed that the stone should be removed from the right ureter immediately and this was done without further delay. The ureter at the site of the stone was found very much enlarged and thickened. Upon opening the ureter and removing the calculus, there was a great gush of dammed-up purulent urine. A small catheter was introduced up the ureter for drainage. The patient made a very good and prompt recovery and further urological studies were then carried out. The ureterostomy tube apparently had passed up the more medial of the two ureters and gradually there was some reduction in the size of the hydro-ureters and hydronephroses. The patient was discharged from the hospital with the ureterostomy tube in place and studies were repeated intermittently. However, the tube accidentally came out, the wound healed with rapidity and with practically no escape of urine. The patient's condition continued to improve. She was entirely symptom free and refused further operative interference for approximately a year. She did, however, return frequently for observation and further urological study. During the course of

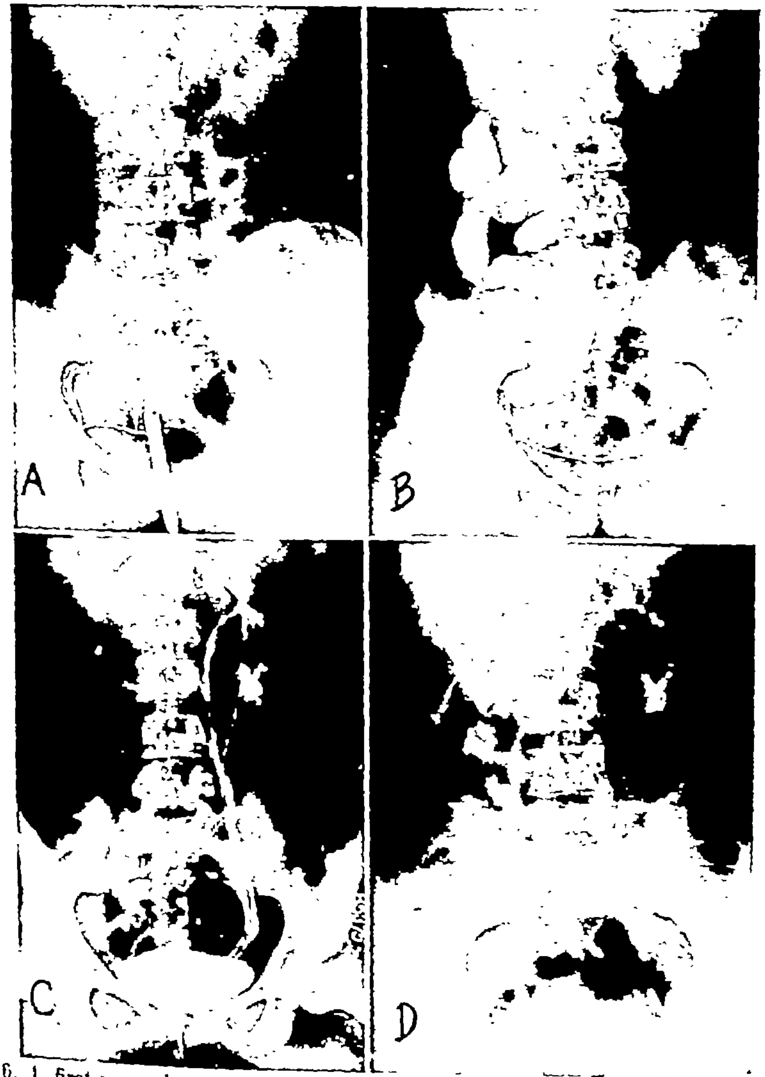


FIG. 6. *A*, first x-ray demonstrating calculus lying low in right ureter at tip of catheter. *B*, demonstrating two large, atypical pelves on right side with ureters joining in lower third. *C*, demonstrating two renal pelves on left side with two separate ureters. *D*, excretory urogram demonstrating, for first time, a third pelvis on right side above the other two.

these studies or approximately three or four months after removal of the ureteral calculus, there appeared in various x-ray films a shadow in the region of the upper pole of the right kidney above the two pelves which had not previously been present. This led us to suspect further additional renal tissue or pelvis which was

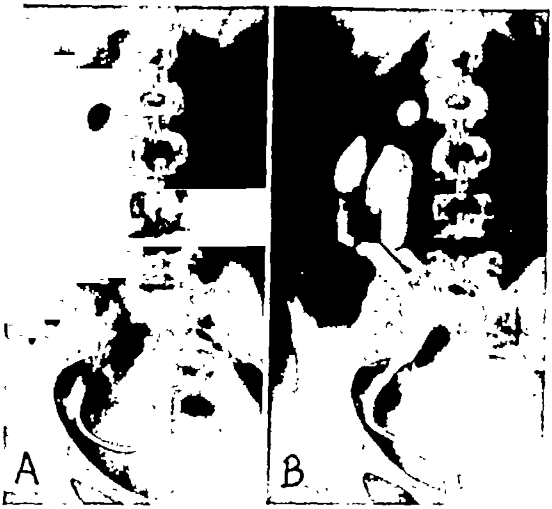


FIG. 7. *A*, flat film with catheter in right ureter approximately a year after original examination. Recurrence of calculi. *B*, right retrograde pyelogram demonstrating two pelves with joining ureters. Calculi apparently in third pelvis and ureter, but impossible to demonstrate by retrograde pyelography.

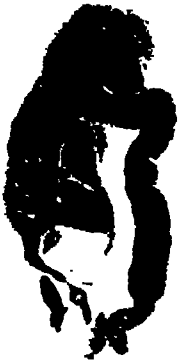


FIG. 8. X-ray demonstration of operative specimen

proven by excretory urography. A repeated search for an ectopic ureter gave negative results. There was not sufficient concentration of the dye to completely outline the ureter leading from the third pelvis. Repeated attempts to outline a third ureter, by retrograde pyelography, met with no success. After a considerable time, however, three fairly large stones, all apparently from this upper pelvis, developed and they moved up and down the ureter freely and without pain.

Finally, a little over a year after her original operation, the patient consented to enter the hospital for further observation and operation. She had started having further attacks of rather severe pain in the right flank accompanied by chills and fever, loss of weight and general malaise. There had been no attacks of pain or discomfort on the left side. Repeated urological study revealed the two left pelves to be essentially normal as to function. The function on the right side was remarkably reduced. See Figure 7. From our studies, we believed that we were dealing with three pelves on the right side and with two ureters from the lower two pelves fusing and a third ureter from the upper pelvis which we could not visualize except faintly in its upper portion by excretory urography. Preoperatively we were of the opinion that we were probably dealing with supernumerary kidneys. At operation, however, it was found that the three pelves were contained in one large capsule and that there were three ureters leading from the pelves, the two lateral of which united about half way down, running from this point to the bladder in one sheath. The third ureter ran separately down to the bladder wall where it apparently united with the other intramurally. There was very little renal parenchyma left in the entire kidney. The whole right renal mass was removed together with the ureters with some difficulty. As might well be imagined, the blood supply was quite anomalous and very copious. The pateient made a very excellent and quick recovery and in the matter of a few months she had gained approximately 20 pounds in weight, the urine became free of infection, acid in reaction, and urinary cultures became negative.

Study of the pathological specimen revealed that there were three separate and distinct pelves with no communication between them. There were three separate ureters with fusion of the lateral two above the bladder. The third ureter apparently fused in the bladder wall, thereby presenting only one ureteral orifice on the right side. See figure 8. This case then can be classified as triplication of the renal pelvis and ureter with fusion of the three ureters or the so called trifid ureter.

CONCLUSION

The incidence and embryology of triplication of the ureter and kidney pelvis has been reviewed and an additional case of this interesting anomaly has been reported.

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THE URETERAL SPLINT IN THE REPAIR OF URETEROPELVIC AVULSION

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Avulsion of the ureter from the renal pelvis during conservative operations upon the kidney is a serious and embarrassing accident. As might be expected, it frequently results in the loss of the kidney. The temptation to perform nephrectomy is strong because of the technical difficulties of repair and the uncertain healing of ureteropelvic anastomoses. Although re-implantation of the ureter in a useful standard procedure for hydronephrosis caused by ureteropelvic obstruction, it is seldom the procedure of choice. It is used when other plastic procedures are not adaptable. In accidental ureteropelvic disruption, the unsubstantial appearance of the torn tissues leads one to despair that they may ever be joined; that they could heal without stricture or even heal at all strains the imagination. It is easily understood that a surgeon confronted by this situation might consider himself unduly bold to attempt repair in the presence of a sound kidney on the opposite side. Of course, the accident occurs infrequently, and its prevention is more important than its cure. Textbooks of urological surgery, mentioning this mishap, advise anastomosis if possible, generally with diversion of the urine by nephrostomy. Few reports and little discussion of this problem can be found; we present this paper because our experience has provided convincing evidence of the value of a splint in ureteropelvic surgery.

We are indebted to David M. Davis, T. E. Gibson, Clark Johnson, Roy Henline, and others for their clinical research in the use of the ureteral splint and to those, including Bailey, Begg, McArthur, and Hyman and Wilhelm, who have written on ureteropelvic anastomosis following avulsion. The report of Hyman and Wilhelm, published in 1940, is particularly instructive, describing 5 cases of avulsion occurring during pyelotomy for calculus with infection. In each case an attempt was made to save the kidney by re-implantation of the avulsed ureter into the renal pelvis. The pelvis and ureter were always found to be severely inflamed and friable, making anastomosis difficult. They concluded that successful re-implantation of a ureter severed from the renal pelvis was based upon: 1) the provision of free urinary drainage by means of a nephrostomy; 2) accurate suture of the ureter to the pelvis without tension; and 3) splinting of the anastomosis with a catheter, in order to immobilize the ureter and to maintain the *stoma*. In two of their cases, where these principles were not observed in full, secondary nephrectomies were required. In a third case, a small splint was used without diversion of the urine by nephrostomy and, although a functioning kidney was maintained, a stricture developed in the ureter. In a fourth case, where a small catheter was used as a splint but nephrostomy was omitted, a normally functioning kidney was eventually obtained after postoperative ureteral dilatation.

Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 28, 1951.

In the fifth case, where all three principles were observed, including the use of a size 12F catheter as a splint, a perfect result was obtained free of complications. These operations were all done before the discovery of antibiotics and before widespread use of the sulfonamides, yet study of the case reports does not suggest that today's chemotherapeutic agents would have been of any help in overcoming the mechanical difficulties encountered.

PREVENTION OF URETEROPELVIC AVULSION

To avoid injury of the ureter, observation of good surgical technique including adequate exposure, careful handling of tissues, and gentle dissection under direct vision is fundamental. The use of a tape around the ureter is a perfectly sound way of exerting traction and facilitating dissection of the upper portion and of the ureteropelvic juncture. When this operative step has been completed, the tape is no longer needed and should be discarded since inadvertent traction upon it has been known to disrupt the ureteropelvic connection.

After a pyelotomy has been made, overenthusiastic probing with clamp or finger in an attempt to withdraw calculi from the calyces may increase the opening in the kidney pelvis to such an extent that the ureter is left hanging by a thread. When stones in the calyces are difficult to reach through the pelvis, a limited nephrotomy is indicated.

Undue traction upon the kidney to bring it into the wound is a contributory factor to ureteropelvic avulsion. There is a particular danger of this in exposing portable x-ray films of the mobilized kidney. In placing the casette behind the kidney, it may be forced down upon the ureter in such a way as to disrupt it.

Finally, the placing of a splint into the ureter can avulse the ureter. In passing a splint, it should be well lubricated, and firm countertraction should be made upon the ureter. When use of a splint is anticipated, the preoperative placing of an inlying ureteral catheter which may be attached to the splint and used to draw it down into the ureter is helpful.

In some cases, particularly those with calculi impacted at the ureteropelvic juncture, and with infection, the tissues are usually extremely friable or even necrotic. In fact, spontaneous rupture of the kidney pelvis may take place. In such cases, the necrosis may defy the best technique so that serious damage to the ureteropelvic juncture at the time of operation is unavoidable. In such cases, it is a measure of caution to make the pyelotomy incision well above the ureteropelvic juncture, but in kidneys with markedly intrarenal pelves this may be impossible.

CASE REPORTS

We have been called upon to treat surgical avulsion of the upper ureter only in the following 3 cases. Although in each case an excellent result was obtained, we have no desire to expand the series. Should avulsion ever happen again, we would apply the same principles in treatment. The cases are similar: In all of them a stone had been impacted at the ureteropelvic juncture for a long time with associated infection, and in each case the pelvis was intrarenal. The pelvic tissues were extremely friable. The function of the kidney was known to be good. The principles used in repair were: 1) diversion of the urine by nephrostomy,

2) use of a large ureteral splint, 3) fixation of the torn ureter as close to the pelvis as possible, and 4) provision for extrarenal drainage by soft rubber tube drain. In no case was it possible to secure accurate anastomosis of the ureter to the pelvis by sutures throughout the extent of the tear; in fact, the ureter was usually sutured to the renal capsule of the hilus (fig. 1). Antibacterial drugs were used; but, although chemotherapy was undoubtedly helpful, its effect was principally ancillary. The effective results are attributed to the great natural propensity of the pelvic tissues to regenerate over a suitable splint when the urine is properly diverted. It is difficult to see how a functional opening could have been obtained without the application of the principles of splinting and diversion when actual anastomosis of the torn tissues was impossible.

Case 1. Miss A. K., aged 50, was found to have a stone 1 cm. in diameter in the renal pelvis with urinary infection for several months. She declined urological investigation or treatment and was able to control her symptoms by intermittent use of sulfonamides. She was otherwise well.

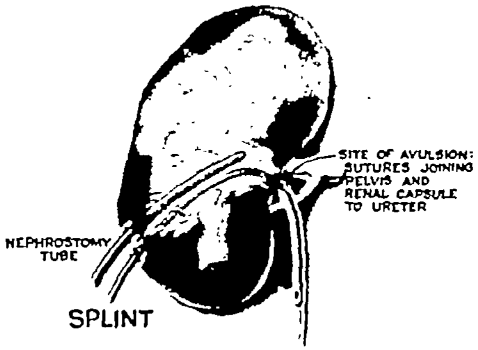
SITE OF AVULSION: SUTURES JOINING PELVIS AND RENAL CAPSULE TO URETER
NEPHROSTOMY TUBE
SPLINT

FIG. 1. In ureteropelvic avulsion, it may be impossible to secure accurate anastomosis, but ureter may be sutured to renal hilus and healing takes place about splint.

On January 11, 1947, pain in the left kidney region for several days associated with nausea and vomiting and fever forced her to enter the hospital. The stone had become impacted at the left ureteropelvic juncture (fig. 2, *A*, *B*). A catheter was passed to the left kidney pelvis and purulent urine under pressure was obtained. The catheter was left inlying. Studies showed that the right kidney was normal.

A left pyelolithotomy was performed on the following day. The kidney was acutely inflamed and inflammatory adhesions and edema were present about the upper ureter and kidney pelvis. The pelvis was almost entirely intrarenal but was exposed by retraction of the posterior lip of the hilus. During blunt dissection of the posterior aspect of the pelvis over the stone, the pelvis was ruptured and the stone extruded spontaneously. This left a ragged defect in the kidney pelvis and ureteropelvic juncture, the edges of which were necrotic. On the anterior aspect, the ureter was attached to the pelvis by a strip of tissue 2 mm. in breadth. The mucosa on this strip was deeply ulcerated. Because the ureter was nearly severed and even the small attached area was severely inflamed, a size 18F Nelson catheter was passed through the kidney parenchyma on a Cabot hook and passed into the ureter for a distance of 10 cm. No attempt was made to close the defect in the pelvis and ureteropelvic juncture, since the strip on the anterior aspect appeared to be strong enough to maintain continuity. Drainage holes had been cut in the intrapelvic portion of the catheter to divert the urine. A soft rubber tube drain was placed down to the pelvis and the wound was closed.

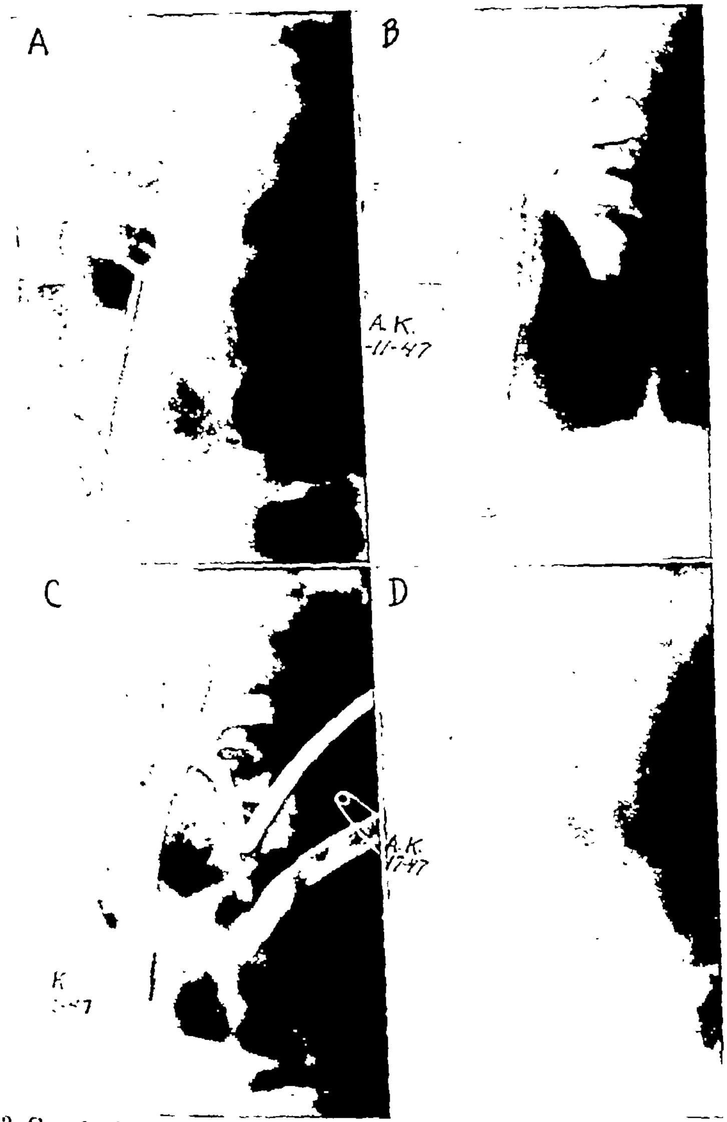

Fig. 2. Case 1. *A* and *B*, preoperative plain film and pyelogram. *C*, nephrostogram on tenth postoperative day; no extravasation. *D*, excretory urogram 9 months later.

The patient was given penicillin and sulfadiazine both before and after surgery. Her course was completely uneventful. After 2 days, urinary leakage from the wound stopped. Some fluid escaped through the wound on irrigation for five more days. On the tenth postoperative day a nephrostogram (fig. 2, *C*) showed an essentially normal kidney pelvis with no extravasation. The tube was removed. Urinary leakage stopped in 24 hours and, on the twelfth postoperative day, excretory urograms were normal.

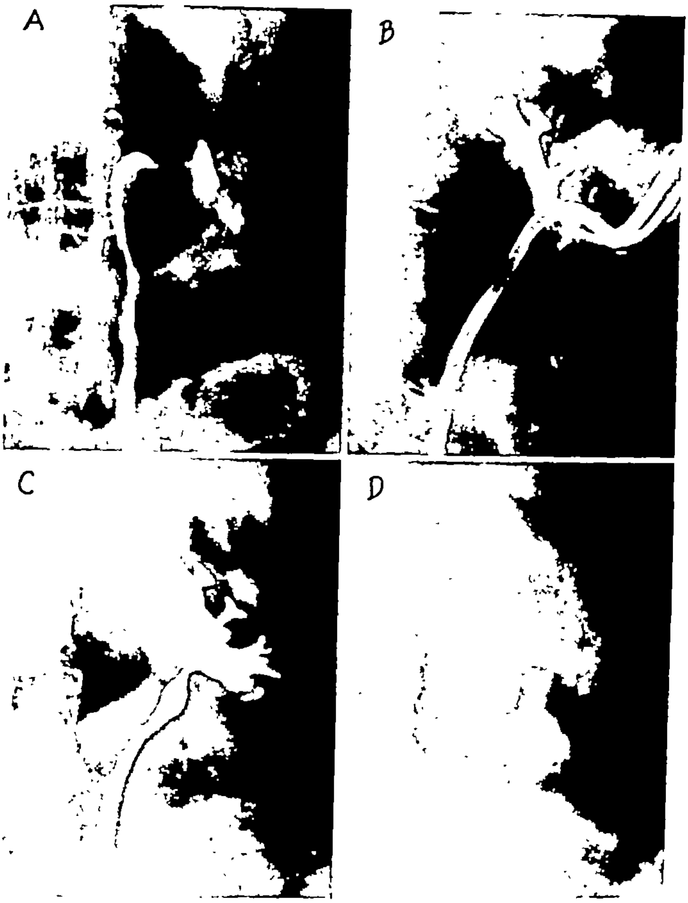

FIG. 3. Case 2. *A*, preoperative pyelogram. Kidney displaced and rotated by large spleen. Stone at ureteropelvic juncture. *B*, nephrostogram on thirty-fifth postoperative day. *C*, and *D*, pyelograms 1½, and 6 months postoperatively.

The patient was relieved of all her symptoms and of the urinary tract infection. She has remained well to date. Excretory urograms taken 9 months after operation were entirely normal (fig. 2, *D*).

Case 2. Mrs. E. D., aged 52, entered the hospital on August 15, 1917 complaining of frequency and burning on urination, an ache in the left kidney region, and a low grade fever for 3 months. She had received three courses of a sulfonamide with temporary relief. For 3 years she had been subject to recurrent episodes of left renal colic with hematuria. In addition, this patient had polycythemia vera for at least 4 years, with moderate impairment of cardiorespiratory reserve and great enlargement of the spleen. She was chronically ill. Urologic study disclosed a normal right kidney. A stone 2 cm. in diameter was impacted at the left ureteropelvic junction (fig. 3, *A*). Moderate hydronephrosis was present, and the urine was heavily infected with A. aerogenes. A stricture at the ureteropelvic juncture was seen below the stone, and the pelvis was almost completely intrarenal. Phenolsulfonphthalein excretion was 20 per cent from the right side and 10 per cent from the left side in 15 minutes.

On August 25, 1947, a left pyelolithotomy was performed. Exposure was hindered somewhat by the necessity of retracting the large spleen away from the operative field. There were many adhesions about the kidney pelvis and upper ureter, and an intrinsic narrowing was present at the ureteropelvic juncture. The pelvis was inflamed and very friable. A posterior pyelotomy was made over the stone and extended down through the stricture at the ureteropelvic juncture. Following the removal of the stone, a size 16F Robinson catheter was passed through a lower calyx on a Cabot hook and an attempt made to introduce it into the ureter. After the catheter had passed a centimeter or two, the ureter became completely separated from the renal pelvis. The avulsion was caused by slipping of the forceps grasping the ureter in making countertraction. The size 16F catheter was passed 8 cm. further down without difficulty. An attempt was made to suture the torn tissues, but they were badly inflamed and would not hold sutures. Besides, the pelvis had retracted well up under the lip of the hilus, so that it was possible to get only one 4-0 chromic suture from the pelvis to the ureter on the anterior aspect. Two other sutures placed superiorly and inferiorly were taken from the ureter to the renal capsule on the lip of the hilus. This left a large defect in the pelvis. Prior to making this crude anastomosis, a size 24F Malecot catheter was put into the kidney pelvis through another lower calyx. A soft rubber tube drain was left down to the renal pelvis and the wound was closed.

The patient was treated before and after surgery with penicillin and sulfadiazine. Her immediate postoperative course was stormy because of pulmonary atelectasis and pneumonia. Urinary drainage continued through the wound for eight days. On the twenty-second postoperative day she was in good condition. A nephrostogram showed a normal renal pelvis with radiopaque substance passing down the ureter around the splinting catheter, but extravasation from the pelvis was also present. The patient shortly afterward ran a low grade fever and developed increasing discomfort in the left flank. On the thirty-fifth postoperative day, a nephrostogram showed no extravasation (fig. 3, *B*) and the splint was removed. Injection of radiopaque solution into the tube drain disclosed the presence of an abscess cavity extending along the lateral border of the psoas muscle to the iliac vessels. This cavity had been drained inefficiently by the soft rubber tube drain, which had become displaced. On the thirty-sixth postoperative day, the abscess was drained through a separate incision. Recovery was then uneventful. The nephrostomy tube was clamped without leakage, so that on the thirty ninth postoperative day it was removed. The patient remained in the hospital 20 days more, primarily for treatment of polycythemia vera.

Studies 1½ and 2 months later (fig. 3, *C*) showed no evidence of urinary tract infection and normal function of both kidneys. A postoperative defect was present in the left kidney pelvis but there was no stricture and drainage was free. Six months after operation she had no urinary symptoms and no abnormal findings on examination of the urine or excretory urography (fig. 3, *D*).

Case 3. Mrs. L. T. S., aged 30, was first seen on September 1, 1949 with the complaints of intermittent pain in the left flank for 1 year, and recurrent urinary tract infection with fever for 3 or 4 months. These attacks were temporarily relieved by sulfonamides and chloromycetin. She had recently emigrated from China and was in a poor nutritional state, as well as suffering from intestinal parasites and anemia. She was 2½ months' pregnant. Urologic studies showed infection in both kidneys with normal kidney function by excretory urography and phenolsulfonphthalein excretion. The right pyelogram was entirely normal. The left kidney pelvis contained a large stone at the ureteropelvic juncture and several small calculi in the calyces (fig. 4, *A*, *B*).

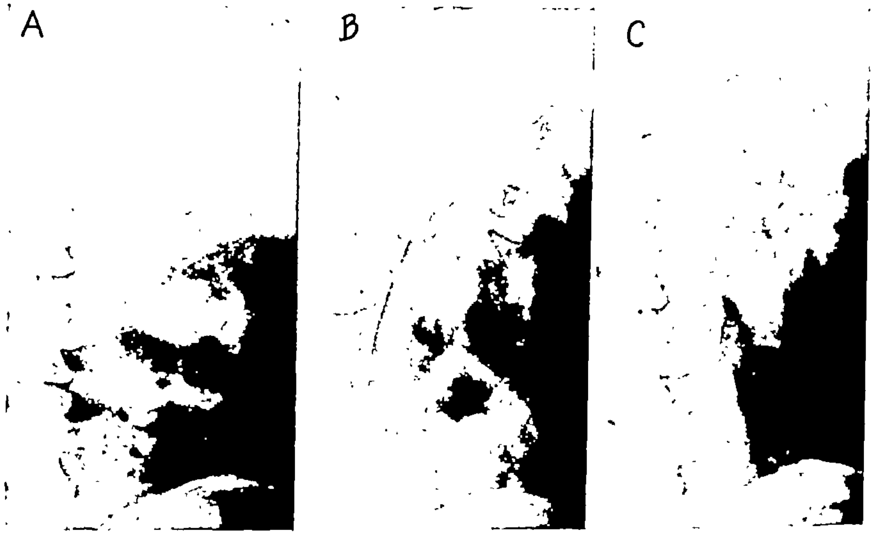

Fig. 4. Case 3. *A* and *B*, preoperative films. *C*, pyelograms 13 months later. No calculi visible on plain film.

Operation was advised, but the patient procrastinated for another month. She was kept on small doses of sulfonamides and treated for the anemia and intestinal parasites. Left nephrolithotomy was finally performed on October 5, 1949. Numerous adhesions were present about the kidney and upper ureter. The kidney pelvis was entirely intrarenal, requiring an incision in the posterior lip of the hilus for exposure. The pelvis was opened between stay sutures and the large stone at the ureteropelvic juncture removed. This stone filled the pelvis and was wedged firmly in place. In removing it the pyelotomy was enlarged by a transverse incision. A finger was passed through the wound in order to find the remaining calculi. Two stones were found in a lower calyx, one in a middle calyx, and another in an upper calyx. The stones in the lower calyx were removed through the pyelotomy. A portable x-ray was used to locate the others, which were then removed through separate nephrotomy incisions. In removing the casette from the wound, the ureter was accidentally avulsed. Prior to this, the pelvis had been considerably lacerated. A size 20F Malecot catheter, to act as a nephrostomy, and a size 16F Robinson catheter, to act as a ureteral splint, were placed as in case 2. The ureter was sutured to the pelvis in three places with interrupted sutures with a fourth suture from the ureter to the lip of the hilus. A soft rubber tube drain was placed down to the kidney pelvis.

The patient received small daily doses of sulfonamides and chloromycetin postoperatively. She did extremely well. Urinary leakage and leakage on irrigation through the wound stopped on the fourth postoperative day. On the ninth postoperative day, the ureteral splint was removed. There was no drainage from the wound and, on the eleventh postoperative day, fluid injected into the nephrostomy tube passed rapidly into the bladder. The tube was removed and the fistula closed in 24 hours.

The patient was discharged on the thirteenth postoperative day. She continued to take 500 mg. of sulfadiazine daily throughout her pregnancy and for 6 weeks after delivery. There was no further difficulty with the urinary tract and her general health improved. She has had no urinary complaints. Since the urine showed no evidences of infection, the sulfonamides were discontinued. She has continued to remain well. Intravenous urograms 13 months later were entirely normal (fig. 4, *C*). A ureteral catheter passed to the left kidney pelvis without difficulty, and there was no residual urine.

DISCUSSION

The fact that these three avulsions occurred during operations on the left kidney in females is not considered significant. There is no doubt, however, that the similar pathologic process, a neglected stone impacted at the ureteropelvic juncture with chronic infection, is significant. The small size of the renal pelvis in each case and its location beneath the renal hilus contributed to the surgical accident. In case 1, the avulsion was caused primarily by the disease process, was almost spontaneous, and could only have been avoided by earlier (or possibly later) operation. The friability of the pelvic tissues might have been decreased by drainage of the renal pelvis for another day or two by an inlying ureteral catheter. Although avulsion was not complete, the ureter remained attached to the pelvis only by a shred of badly infected tissue, and it is difficult to see how satisfactory healing would have taken place had a splint not been used.

In case 2 the lesion was somewhat similar prior to the attempted passage of a splint, which completed the avulsion. The need of a splint in the second case was indicated both by the peri-ureteral inflammation and by the presence of intrinsic narrowing at the ureteropelvic juncture. A technical error was committed in failing to grasp the ureter sufficiently firm with forceps to relieve the tension on the thin bridge of tissue. A smaller splint might have obviated this accident but our experience with intubated ureterotomy for ureteropelvic juncture obstruction indicates that the best splint to use is the largest one that can be passed.

If a splint size 14F or larger can be used, such plastic operations are usually successful; but if only a size 12F or smaller splint can be passed, the results are usually disappointing. The slow healing in this second case was probably also directly related to inefficient extrarenal drainage. The inner end of the soft rubber drainage tube was either improperly placed at the time of surgery or became displaced in the early postoperative period.

In the third case, although a tape was not left around the ureter, avulsion occurred from a sudden tug during the making of portable x-ray films which, incidentally, proved invaluable in locating stones which did not show on the preoperative plain x-ray film. This procedure, however, is one that is apt to divert the attention of the surgeon away from the organ and onto the casette. Contributing factors to the injury were the pathologic process itself, the necessity for a wide pyelotomy in order to remove the stones, and further injury to the renal pelvis by the finger manipulation incident to the location and extraction of the calyceal calculi.

Another factor in these cases but somewhat difficult to evaluate is the action of sulfonamides and antibiotics. Although these drugs were no doubt of considerable benefit in connection with the surgery, it is difficult to escape the impression that were these suppressive agents not available, definitive surgical treatment would have been carried out sooner in each case. This might have avoided the weakening of the pelvis by long continued pressure of the stones which hindered the operative treatment and contributed to the injuries.

CONCLUSIONS

The basic principles in the surgical repair of ureteropelvic avulsion in the order of their importance are: 1) diversion of the urine, 2) use of an inlying splint, 3) approximation of the torn edges as well as possible, and 4) adequate provision for extrarenal drainage of extravasated urine. Although a careful anastomosis between the severed tissues throughout their circumference is desirable, it is not often possible. Fixation of the ureter to the hilus of the kidney is one way of keeping the edges more or less approximated and preventing retraction of the ureter downward. In the current argument between those using splints and those opposing them, we feel that the results in these three cases provide overwhelming support for their use. The regenerative power of the ureter and kidney pelvis is truly remarkable, but we could not expect healing in our three cases where the tissues were widely separated or hanging only by shreds without the use of a splint.

SUMMARY

Ureteropelvic avulsion occurring during conservative renal surgery can be successfully repaired with complete restoration of renal function by the use of a ureteral splint and proper diversion of the urinary stream.

Accurate edge-to-edge anastomosis of the avulsed tissue is desirable but often impossible, and, fortunately, unnecessary.

Three cases of successful repair of ureteropelvic avulsion clearly demonstrate that a large splint will allow healing of the large defects in the pelvis and upper ureter which occur as a result of this injury. Also, by inference, a splint is important in the repair of defects found in the surgical treatment of ureteropelvic obstructions in general.

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USE OF PLASTIC (POLYETHYLENE) TUBING IN SURGICAL MANAGEMENT OF URETEROPELVIC OBSTRUCTIONS

FREDERICK C. SCHLUMBERGER AND P. PAUL RIPARETTI

The treatment of hydronephrosis due to ureteral or to ureteropelvic obstruction has been discussed widely in the past few years.[1, 2, 3, 4, 5] This interest is perhaps a corollary of increased attention to reconstructive surgery and to conservation of essential organs.

Recent developments in chemistry have placed in our hands materials that promise to enhance reconstructive operations from the standpoints of both technical convenience and ultimate physiologic effect.

During the past 20 years about twenty-five types of reconstructive procedure for the treatment of hydronephrosis due to ureteral or to ureteropelvic obstruction have been introduced. It was David M. Davis,[6, 7] in 1943, however, who revitalized our thinking and the concept of ureteral intubation in these surgical procedures.

The purpose of this discussion is to record our clinical experience with polyethylene tubing for intubation of the ureter. The observations were made in 11 cases under our personal supervision at Wadsworth General Hospital, Veterans Administration, Los Angeles, and at Saint John's Hospital, Santa Monica, Calif. Other cases were observed indirectly on the Urologic Service at Wadsworth General Hospital and are not referred to specifically in this paper.

Polyethylene was first produced by the British, in 1936; commercial production was started in the United States in 1943. It is a long chain polymer of ordinary paraffin wax, having a molecular weight of over 18 thousand. It is a flexible—but not limp nor rubbery—semitransparent, nonradiopaque material which is unusually resistant to chemical action.

In our experience polyethylene tubing presents certain advantages for ureteral intubation not demonstrated by other materials from the viewpoints of the surgeon's convenience, the patient's comfort and, to some degree, the final functional result. It is available as small, thin-walled tubes that are flexible and easily cut by scissors or scalpel. It maintains its shape and natural resilience even when left in animal tissues over a long period of time. Animal experiments conducted by Grindlay,[8] Mann and Grindlay,[9] and Ferris and Grindlay,[10] of Roches-

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 28, 1951.

[1] Ballenger, E. G. and McDonald, H. P.: J. Urol., **47:** 203-208, 1942.

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[10] Ferris, D. O. and Grindlay, J. H.: Proc. Staff Meet., Mayo Clin. **23:** 385-390, 1948.

ter, Minn., and by Ingraham, Alexander and Matson [11], [12] of Boston, indicate that polyethylene does not produce a foreign body reaction and that it is well tolerated by nerve tissue, bone, muscle and mucous membranes. Pus and mucus do not adhere to its surface, and inorganic salts do not precipitate on the walls of the tubes—which factor in itself has great appeal to the urologist. These attributes would seem to make it an extremely desirable material for ureteral splinting, since the splints must be left in place for rather long periods of time following reconstructive procedures.

PREPARATION OF POLYETHYLENE SPLINTS

Careful preparation of the splinting material before surgery is essential. It is always good planning to prepare splints of various sizes of tubing. Polyethylene tubing No. 320 and No. 330, with inside diameters of 2.69 mm. and 2.92 mm., have proved most useful. The length of splint required in the individual case should be estimated with care. The distance to the renal pelvis is measured by passing a ureteral catheter; measurements are taken also from the roentgenograms.

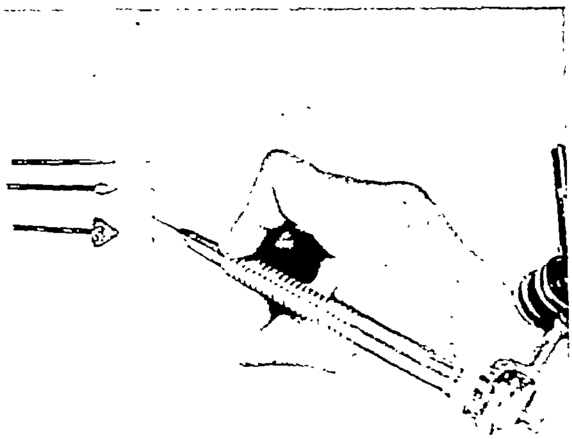

FIG. 1. Dental drill and burr for perforation of polyethylene tubing which is to serve both as a ureteral splint and for drainage.

One should anticipate whether the tube is to be used entirely as a splint or whether it is to serve also in establishing drainage of urine. In the latter instance perforations must be made in the tubing. We first used a heated dissecting needle for this purpose. Since polyethylene becomes amorphous about 115C, the temperature of the needle had to be carefully controlled. This method produced some roughness around the edges of the openings, however, and it was difficult to make them small enough to avoid kinking of the tubing at the point of perforation. Our present method of perforation employs a dental drill and a dental burr

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[11] Ingraham, F. D., Alexander, E., Jr. and Matson, D. D.: New Eng. J. Med., 236: 362–368; 402–407, 1947.

[12] Ingraham, F. D., Alexander, E., Jr. and Matson, D. D.: J. A. M. A., 135: 82–87, 1947.

(fig. 1) with which is obtained a smooth, cleancut perforation 1.40 mm. in diameter—the exact desired size, accommodating a 17 gauge needle. These small, cleancut perforations do not impair the flexibility of the tubing; kinking of the ureteral splint will not occur if reasonable care in technique is observed. The number and position of the perforations vary according to whether only the area of the pelvis or both the pelvis and the ureter are to be drained. The splint then is ready for sterilization.

Sterilization. Because of its low melting point, polyethylene cannot be sterilized by autoclaving. Boiling in water does not change its properties except that it retains the shape in which it is placed on boiling. Cold sterilization, thus, is necessary and has proved satisfactory. A 1 to 1000 aqueous solution of zephiran chloride (benzalkonium chloride) has been used for this purpose. The splints are placed in the solution at body temperature about two hours before surgery. Polyethylene is chemically stable and is not affected by zephiran chloride solution in any way.

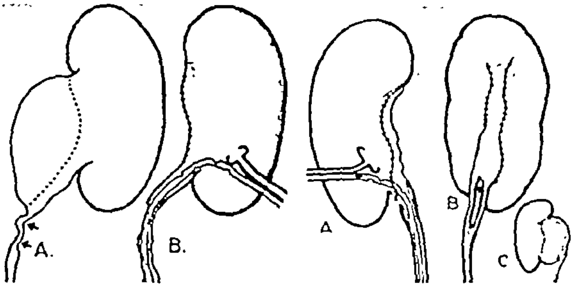

FIG. 2. Two methods of pyeloplasty

TECHNIQUE OF PYELOPLASTY EMPLOYING POLYETHYLENE SPLINT

A polyethylene splint or any other type of splint is chiefly a mechanical adjunct to surgical reconstruction of the renal pelvis and the ureteropelvic area, or to surgical relief of ureteral obstruction. The type of pyeloplasty or ureteroplasty may be one of personal preference. As a rule, choice of procedure must await the observations at surgery.

Two methods of pyeloplasty have been used by us for surgical reconstruction of the renal pelvis and the ureteropelvic junction. They constitute variations of methods described by several authors and cannot be identified by any specific name (fig. 2). We have found them to be applicable to the majority of cases in which resection of the redundant portion of the pelvis is necessary.

Before surgery a No. 6 ureteral catheter is passed to the renal pelvis. We believe that a thorough and orderly dissection of the renal pelvis, the ureteropelvic area and the upper portion of the ureter is essential. A complete pelviureterolysis must be done, with division of all fibrous bands and accessory vessels. If there is a large redundant renal pelvis with much overhang and a high ureteral insertion, resection of the redundant portion of the pelvis and reconstruction should be accomplished. This is done not merely for the sake of appearance, but is prerequisite to proper reconstruction of the ureteropelvic outlet and its placement in a dependent position so that the best possible drainage may be established.

The nephrostomy tube then is placed in a convenient position. To obtain best results, we believe that the splint alone should not be relied on for drainage, even though nephrostomy may necessitate sacrifice of a small amount of renal tissue. We have tried various types of catheter as nephrostomy tubes, but have returned to the use of the Pezzer as the most practicable. Polyvinyl plastic catheters proved unsatisfactory for this purpose because of their greater thickness of wall and their lack of flexibility. Recently, however, considerable improvement has been effected in polyvinyl catheters of the de Pezzer and Malecot types; therefore we anticipate a retrial, since all the advantages demonstrated by polyethylene pertain also to polyvinyl.

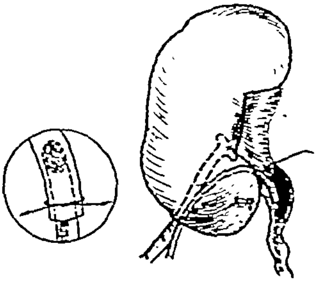

FIG. 3. Diagram of ureteral polyethylene splint being anchored to ureteral catheter for passage down ureter.

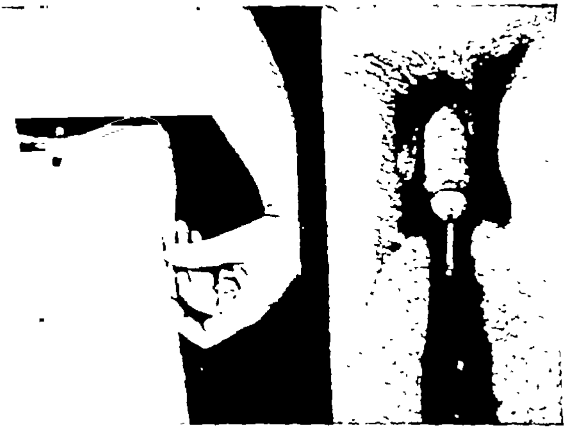

FIG. 4. Ends of polyethylene splint are brought to outside and anchored at points of emergence. Positions at flank and at penile urethra are illustrated.

The ureteral polyethylene splint is passed, adjacent to the nephrostomy tube, into the renal pelvis where it is sleeved over the end of the ureteral catheter passed to the renal pelvis before surgery (fig. 3). The plastic tubing is anchored to the ureteral catheter by means of a black silk suture. The catheter then is withdrawn down the ureter and out through the penile urethra; the polyethylene splint is detached and anchored to prevent retraction (fig. 4). If the end of the splint is allowed to rest within the ureter a stricture may form at the point of contact. Furthermore, should the end emerge from the ureteral orifice and rest on the trigone, a great deal of vesical discomfort is produced. Withdrawing the polyethylene tubing completely out through the penile urethra has been, by far, the most satisfactory procedure according to our observation. The splint thereby is placed in the most comfortable position for the patient anc we are permitted complete control of the splint at all times.

The remainder of the renal pelvis is closed. The strictured area at the ureteropelvic junction is incised through all layers and is left open, as advocated by Davis.[6, 7] In order to maintain the ureter in a straight course and to correct any redundancy, a nephropexy is done. The ureter is covered in all areas with fat, if possible. The wound is closed with the nephrostomy tube and splint emerging at the same point from the flank.

It has been our experience that, unless unusual circumstances exist, any type of splinting tube should remain in place about 28 days. A pyelo-ureterogram then is made, instilling the contrast medium through the nephrostomy tube. If complete healing and a well formed ureteropelvic outlet are demonstrable, the nephrostomy tube is removed on the thirtieth day.

TABLE 1

CASE	SEX AGE	PREOPERATIVE			POSTOPERATIVE			
		Urine	Capacity pelvis	Condition present	Infection	Capacity pelvis	Period observed	Result
1	M-30	Not infected	55–60 cc	Up. obs. l.	None	14 cc	4½ mos.	Fair
2	M-38	Not infected	40–45 cc	Up. obs. r.	None	11–12 cc	4½ mos.	Good
3	M-32	Not infected	70–75 cc	Up. obs. l. calculi	Proteus	16 cc	4 mos.	Fair
4	M-32	Infected	65–70 cc	Up. obs. l.	Proteus	20–22 cc	3 mos.	Poor
5	M-30	Not infected	40–50 cc	Up. obs. r. vessel	None	11 cc	16 mos.	Good
6	M-33	Not infected	36–40 cc	Up. obs. l.	None	12 cc	18 mos.	Good
7	M-22	Not infected	40–45 cc	Up. obs. r.	None	6–8 cc	10 mos.	Good
8	M-26	Infected	35–40 cc	Up. obs. r.	None	8–10 cc	12 mos.	Good
9	F-24	Infected	22 cc	Up. obs. ptosis r.	None	6–8 cc	12 mos.	Good
10	F-32	Infected		Diverticulum ureter r. calculus	None		5 mos.	Good
11	F-22	Infected		Up. obs. r. ptosis	None		8 mos.	Good

REVIEW OF CASES

All patients were young adults; their average age was 29. There were 8 men and 3 women. In 7 patients the right kidney was involved and in 4, the left. A similar condition could be demonstrated in the opposite urinary tract in 4 patients, but to a lesser degree (table 1).

Ten patients had ureteropelvic obstructions. Nine were of the intrinsic type, some being associated with fibrous bands; the obstruction in 1 case was produced by a large aberrant vessel. The eleventh patient of the series had a ureteral diverticulum containing a calculus at the junction of the upper and middle thirds of the right ureter.

Surgical reconstruction of the ureteropelvic area and the renal pelvis was followed by complete symptomatic relief in 8 instances (72.7 per cent), improvement in 2 instances (18.1 per cent) and in 1 (9.0 per cent) the symptoms were not relieved to any extent. Roentgenologic and functional studies indicated good results in 5 patients (fig. 5), fair in 5 others, and no change in 1. Further improvement is anticipated in some of the cases in which short periods of time have elapsed, as yet, since operation.

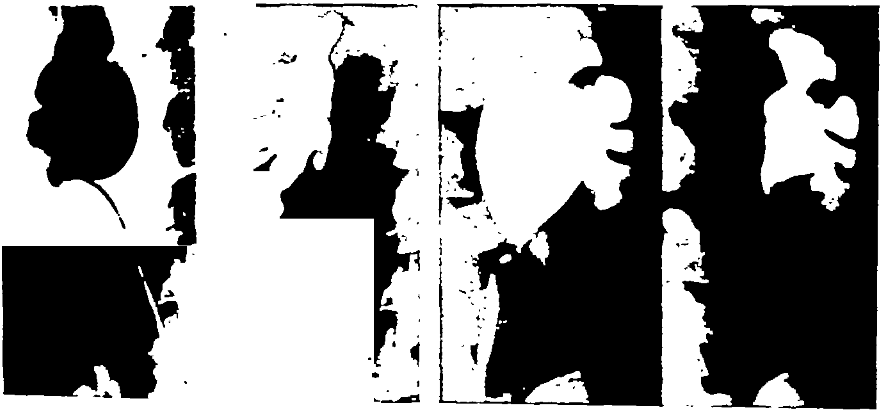

FIG. 5. Preoperative and postoperative retrograde pyelograms in 2 patients in whom results were classified as good.

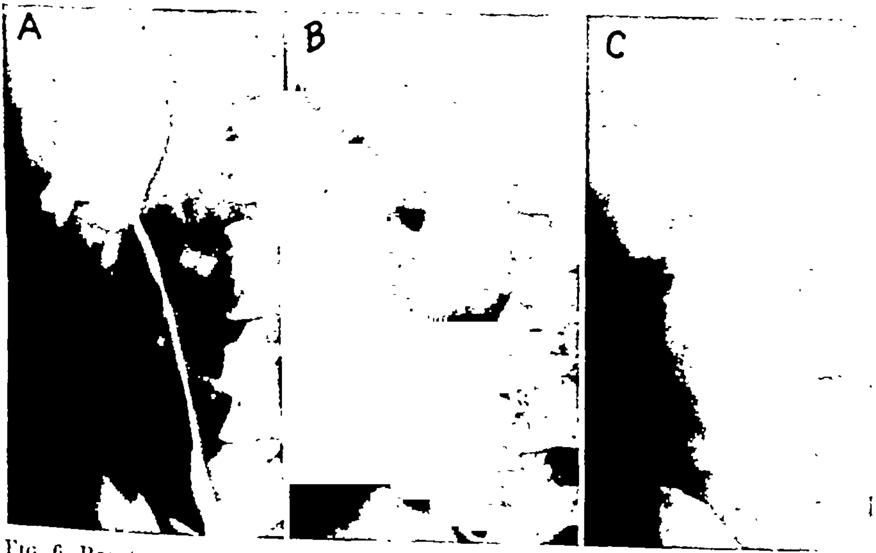

FIG. 6. Roentgenograms in case in which complication of calculus formation was encountered. Illustration at right indicates final satisfactory result.

Infection of the urinary tract was present in 5 cases before operation, and in all during convalescence. Infection was demonstrable 4 months postoperatively in only 2 instances. Proteus vulgaris was the offending organism in both persistent cases. It is our opinion that it is impossible to prevent infection of the intubated kidney and ureter even with the improved methods of antibacterial therapy currently available.

There was one instance of calculus formation (fig. 6), which became demonstrable about three months after operation. The patient had a rather large accessory vessel which supplied a portion of the lower pole of the kidney. This was divided and a calculus formed in the lower calyx at the point of entrance of the nephrostomy tube. Some necrosis may have taken place at this site, forming the ground work for calculus formation. A subsequent operation accomplished removal of the calculus and a good functional result obtained.

Polyethylene tubing No. 320 or No. 330 was used for intubation of the ureter in all of the 11 cases. In 6 instances the splint was passed from the flank through the entire ureter, bladder and penile urethra and was tolerated well by the patients. Little vesical irritation was experienced after the first three or four days and all 6 patients voided around the splint without difficulty after becoming ambulatory. It was found necessary to pass a small silk-woven catheter alongside the urethral portion of the splint for drainage of the bladder while the patients were confined to bed. There was minimal urethral discharge. Urethral irritations, as commonly observed with the use of rubber inlying catheters, were not in evidence, suggesting that less tissue reaction is caused by the polyethylene splint. Mild epididymitis appeared in 1 patient on the twenty-sixth postoperative day; the splint was removed.

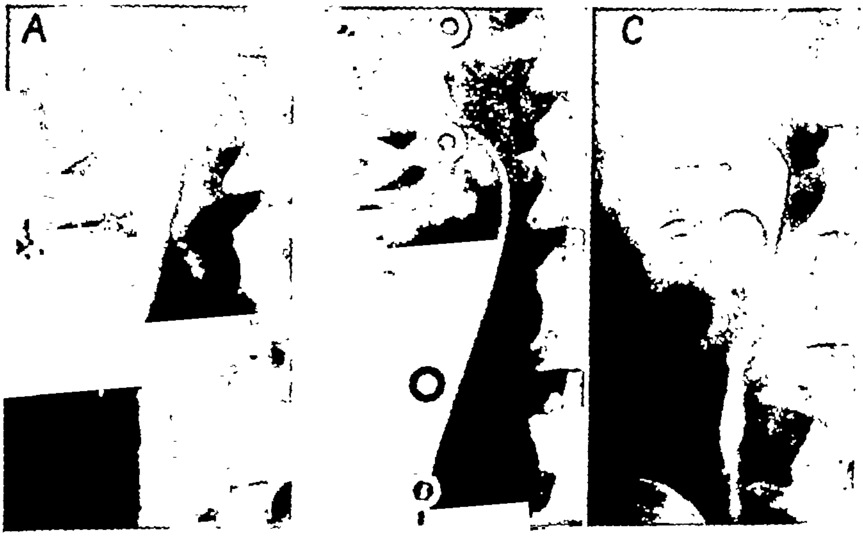

FIG. 7. A, preoperative roentgenogram illustrating ureteral diverticulum with calculus. B, roentgenogram 10 weeks after operation in which air shadow suggests that polyethylene splint is still within renal pelvis and ureter. C, final result 30 days following removal of splint.

Even though polyethylene tubing has great tensile strength, it is light in weight so that early ambulation with comfort can be instituted because the patient is scarcely aware of the presence of the splint.

Several advantages and one disadvantage of the polyethylene ureteral splint were demonstrated in 1 case. The patient was a 32 year old woman who had a diverticulum of the ureter at the junction of the upper and middle thirds of the right ureter; the diverticulum contained a small calculus. There was some ptosis of the kidney and also a moderate amount of pyelectasia with much infection (fig. 7, *A*). The calculus was removed and the diverticulum resected, leaving a considerable ureteral defect. A nephrostomy was done and a polyethylene tube was placed in the ureter with the end of the splint resting in the lower third of the ureter, near the bladder. This tube was used entirely for splinting purposes and was not perforated for drainage of urine.

On the seventh postoperative day the ureteral splint was no longer seen appearing at the flank, although the ties by which it had been attached to the nephrostomy tube still were in place. It was assumed the splint had been pulled out inadvertently at some time while the dressing was being changed. The nephrostomy tube was left in place for another week and pyelography, the contrast medium being instilled through the nephrostomy tube, demonstrated an irregular but intact ureter. The nephrostomy tube then was removed. The opening in the flank healed promptly. We believed that the splint, if it had been left within, would have prevented such rapid closure of the wound, thus we were almost convinced that it had been removed.

The patient continued to be comfortable with the exception of a rather severe pyuria which, however, responded favorably to urinary antiseptics. The right ureter was catheterized at regular intervals with considerable difficulty. About 6 weeks after surgery irregularity of the ureter was noted on the pyelogram and an air shadow was seen to course through the area of the pelvis and portions of the ureter. This shadow had the exact contour of the polyethylene splint (fig. 7, *B*), and we suspected that it still remained within the ureter. Seventy-two days after the first operation, therefore, the incision, which had completely healed, was reopened: The end of the polyethylene tube was found about 4 cm. below the surface of the skin. The splint was followed for a short distance and the ureter was exposed: A slight amount of tissue reaction was evident, the ureter was somewhat thickened, but quite pliable, and the ureteral defect was completely healed. The splint was removed. Subsequent functional studies and roentgenograms indicated that a complete recovery could be anticipated after eradication of some residual infection of the urine (fig. 7, *C*).

DISCUSSION

The case just described illustrates well the minimal tissue reaction produced and the comfort with which a polyethylene splint is tolerated. It also brings to our attention the outstanding disadvantage of the material: If it were radiopaque, the complication encountered in this patient could have been avoided. The advisability of bringing both ends of the splint to the outside is emphasized. Had this been done, contrast media instilled into the splint would have resolved the question.

Let us devote our attention for a short time to the condition of the splint after its removal from the ureter. It had been within the ureter for seventy-two days: The material had remained chemically stable and had maintained its shape and its natural resilience. In every case in the series the splint was free of evidence of "liming" or precipitation of urinary salts, of mucus secretions and of small particles of tissue—so often observed on splints of other materials. In splints perforated for urinary drainage, the inner surface of the lumen, as well as the outer surface, was free of any type of deposit (fig. 8). We believe that irrigation of the nephrostomy tube or of the splint should be reduced to the practicable minimum to permit rapid healing with little formation of scar tissue. Thus, in this series, no special effort, other than use of oral medication, was made to prevent precipitation of urinary salts or other debris.

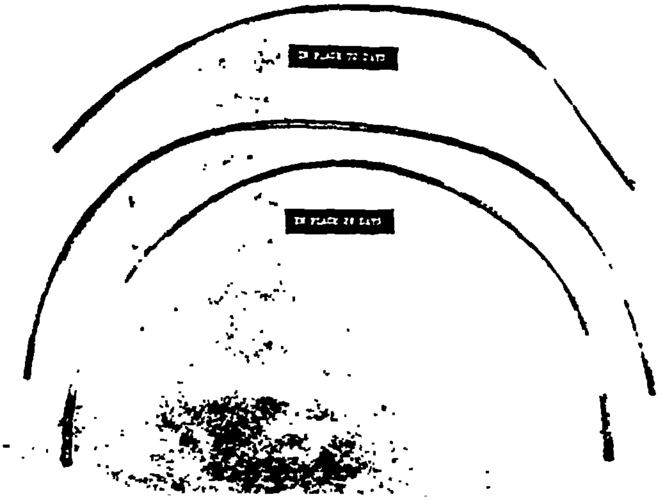

FIG. 8. Photograph of polyethylene splints removed from 3 patients; lack of deposit on tubes is demonstrated.

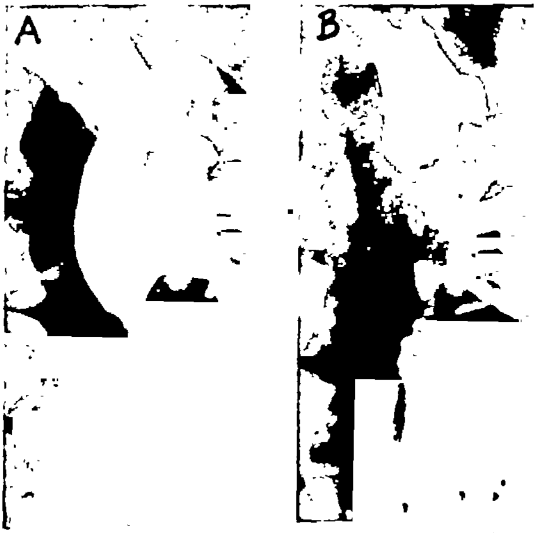

FIG. 9. Preoperative roentgenogram (left) and that taken 3 months after operation (right) indicating poor result.

This type of splint could be salvaged and used again; however, this is not necessary since polyethylene is readily available and is relatively inexpensive.

Perfection never has been attained and a poor result occasionally will be encountered. Failure may be due, in part, to error in judgment. Our enthusiasm leads us to select cases for reconstruction that are not amenable to this type of procedure and that require nephrectomy. We must keep in mind, when considering surgery, that our first obligation to the patient is to preserve that which sustains life.

One should not become discouraged and judge a result poor until sufficient time has elapsed and proper postoperative care has been given; this may require six to eight months. Figure 9 illustrates a poor result three months after operation. Possibly, a few months hence, the condition may be found to be improved; perhaps a secondary nephrectomy may become necessary.

SUMMARY AND CONCLUSIONS

The physical and chemical properties of polyethylene, particularly in relation to reciprocal effects of contact with living tissues, are reviewed.

Eleven cases of ureteropelvic and ureteral obstruction with varying degrees of pyelectasia and caliectasia are presented.

The surgical sequence for correction of these conditions and the technique in the use of plastic polyethylene tubing for intubation of the ureter are discussed.

Clinical observations in this series lead us to conclude that polyethylene tubing demonstrates certain properties that render it superior to other materials for ureteral intubation. It lends itself to the surgeon's convenience, it enhances the patient's comfort, and it facilitates the achievement of a good functional result.

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URETERAL INJURY BY TRANSURETHRAL ELECTRORESECTION AND COAGULATION

JOHN P. DAVIS

Severe and irreparable damage may result to a ureter by accidental, careless, or over-enthusiastic application of the high frequency current used in transurethral electroresection and coagulation. This type of ureteral injury is almost certainly more common than is indicated by the literature. In 1940, Rusche and Bacon, in an otherwise excellent and apparently complete table classifying ureteral injury, failed to mention specifically injury to the ureter by transurethral or transvesical use of the high frequency current. In a recent paper on the subject, O'Conor notes the paucity of the literature.

Opinions seem to differ sharply concerning the effect of the high frequency current on the ureteral orifice. Randall and Uhle, in a paper on transvesical diathermy in the treatment of carcinoma of the bladder, quote Counseller and Braasch as saying that, despite the fact that the ureteral ostium in some of their cases was included in the electrocoagulation, "complete healing occurred in every instance, leaving a clean scar with the ureteral orifice occupying a depression in the scar." On the other hand, Bumpus and Silver, writing on a similar subject, state, "In the transvesical series, a ureteral orifice was included 29 times in the cautery destruction, and in 10 it was considered a decided factor in an unsatisfactory convalescence, if not a decided cause of the patient's death." Randall and Uhle, in 2 of their own cases, found that chronic pyelonephritis occurred secondary to contracture of the ureteral orifice. One had a recurring pyonephrosis which spontaneously emptied itself into the bladder. Concerning the second, in whom death followed 8 months after operation, autopsy revealed that, "Both ureteral orifices were stenosed with resultant bilateral hydronephrosis." They listed acute pyelonephritis and chronic pyelonephritis as two of the three most important complications of diathermy treatment of the bladder, and fistula between the bladder and the vagina or rectum as the third. The fact that these authors mention this complication would indicate that they were impressed with the destructive potential of the high frequency shortwave current.

Further evidence of danger inherent in this current was shown by Caulk in his report of experiments using a thermocouple to determine tissue temperature. At a distance of 1 cm. from the point of application of 1,100 ma. current in the prostate gland for $1\frac{1}{2}$ min., the temperature was recorded as rising from 39.3C to 63.0C. What this means can be readily understood if it is remembered that the thermal death point of tissue cells is approximately 45 to 47C that, at present, currents of 4,000 ma. are in common use.

Barnes, in his excellent monograph, *Endoscopic Prostatic Surgery*, calls attention to the possibility of ureteral injury and postoperative fibrosis and gives some pertinent suggestions relative to treatment. But numerous other authors writing in detail on the technique of transurethral electroresection of the prostate gland

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 28, 1951.

fail entirely to mention the possibility of injury to the ureter. Still other essayists writing specifically about the complications and untoward sequelae of this procedure have not included this type of injury.

While our experience has shown that, occasionally, one or both ureteral orifices may be resected with the high frequency current without harmful effects either immediately or later, I cite the following 5 cases in which there was injury to illustrate types of damage that might occur. In 4 of these cases, the ureteral injury resulted from transurethral electroresection of the prostate gland; in the other, from transurethral electroresection of a bladder carcinoma.

CASE REPORTS

Case 1. A white man, aged 67, had a transurethral resection of the prostate gland February 14, 1950. With a 28F Stern-McCarthy resectoscope, 43 gm. tissue was removed, with a final diagnosis of benign hypertrophy of the prostate gland. A No. 24 Foley 30 cc bag catheter was left indwelling postoperatively.

The gross findings described before surgery were: by rectal examination, the prostate gland was found to be enlarged, grade 2, in both lateral lobes, and of benign consistency. Cystoscopy disclosed that the enlargement involved all three lobes; the median, grade 1, and the laterals, grade 2. Enlargement was intra-urethral and intravesical. The laterals pointed slightly anterior to the verumontanum. There was bladder trabeculation, grade 4, with cellule formation, grade 2. The ureteral orifices were not mentioned in this description. Preoperative examination of the urinary tract by excretory urograms revealed no abnormalities of the upper urinary tract (fig. 1, *A*).

Postoperative course: Highest temperature, 99.2F, pulse, 86; no trouble with postoperative bleeding. The catheter was removed at the end of 72 hours and the patient went home the next day. He made two visits to the office, the first on March 6 and the second on March 20, 1950. He had no complaints. At the second visit, a 24F sound passed readily. The urine was grossly clear. There was no residual.

Almost exactly one year later, the patient returned to the office, with the complaint of painless hematuria for one day. The urine was negative except for slight gross hematuria. At cystoscopy, the right ureteral orifice could not be found. However, in its region, recurrent peristaltic-like retractions could be discerned. Intravenous indigo carmine did not help to locate this ureter. The left ureter was catheterized readily. The results of retrograde left pyelogram and indigo carmine function test were normal (fig. 1, *B*). Excretory urograms revealed right hydronephrosis and hydroureter, grade 2, with obstruction at the ureterovesical junction (fig. 1, *C*). The blood pressure was 160/86, approximately the same as preoperatively.

The case illustrates injury to the right ureteral orifice by transurethral resection of the prostate gland with gradual development of stenosis of the ureteral orifice totally without symptoms for one year. Treatment consisted of transurethral electroresection of a ureterocele resulting from the stenosis (fig. 1, *D*).

Case 2. A white man, aged 63, had a transurethral resection of the prostate gland on December 16, 1940. With a 28F Stern-McCarthy resectoscope, 37 gm. of benignly hypertrophied prostatic tissue was removed.

The preoperative cystoscopic findings were: lateral lobe prostatic hypertrophy, grade 1; median lobe prostatic hypertrophy, grade 3. The median lobe was well inside the internal vesical sphincter, completely obscuring the trigone and ureteral orifices. The postoperative course was uneventful. The patient left the hospital on the sixth postoperative day, voiding well and without residual urine. Six weeks postoperatively, the urine was completely clear. A 24F sound passed readily. The blood pressure was 128/70.

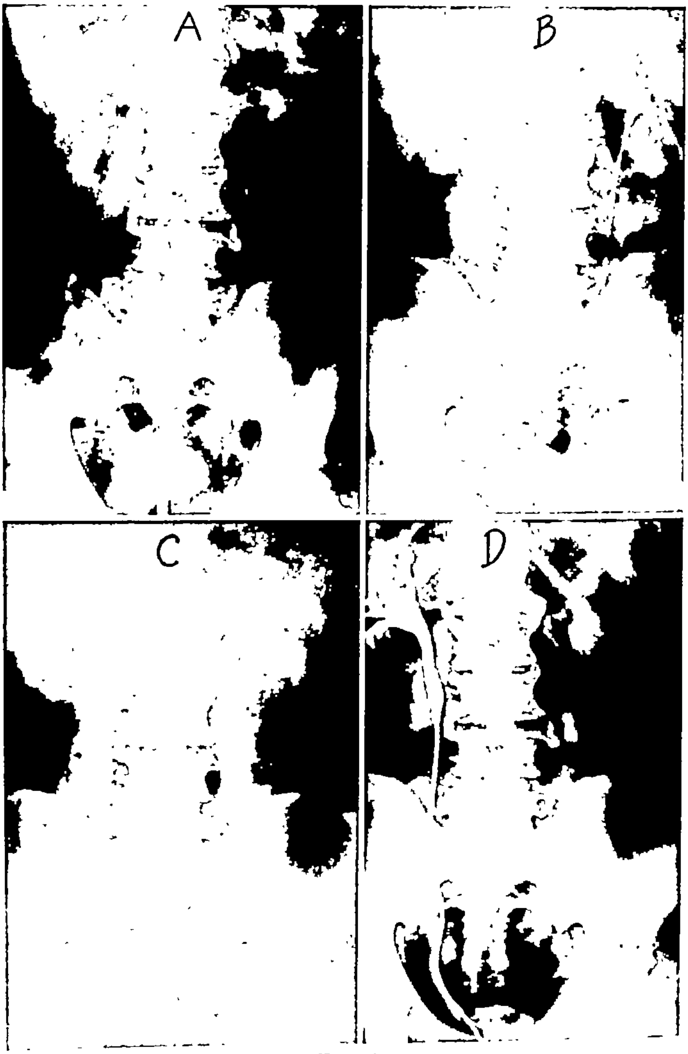

Fig. 1

The patient was not seen again until January 1947, seven years postoperatively, at which time his complaint was of nocturia three times. Excretory urograms then showed slight retention of dye in both ureters, the left being worse than the right (fig. 2, *A*).

The patient was next seen in August 1948, twenty months later. He complained of colicky pains in the left flank, radiating toward the bladder. Findings were an occasional white blood cell in the urine, and delayed function of the left kidney with left hydronephrosis, grade 2, revealed by excretory urograms (fig. 2, *B*). No calculus could be demonstrated.

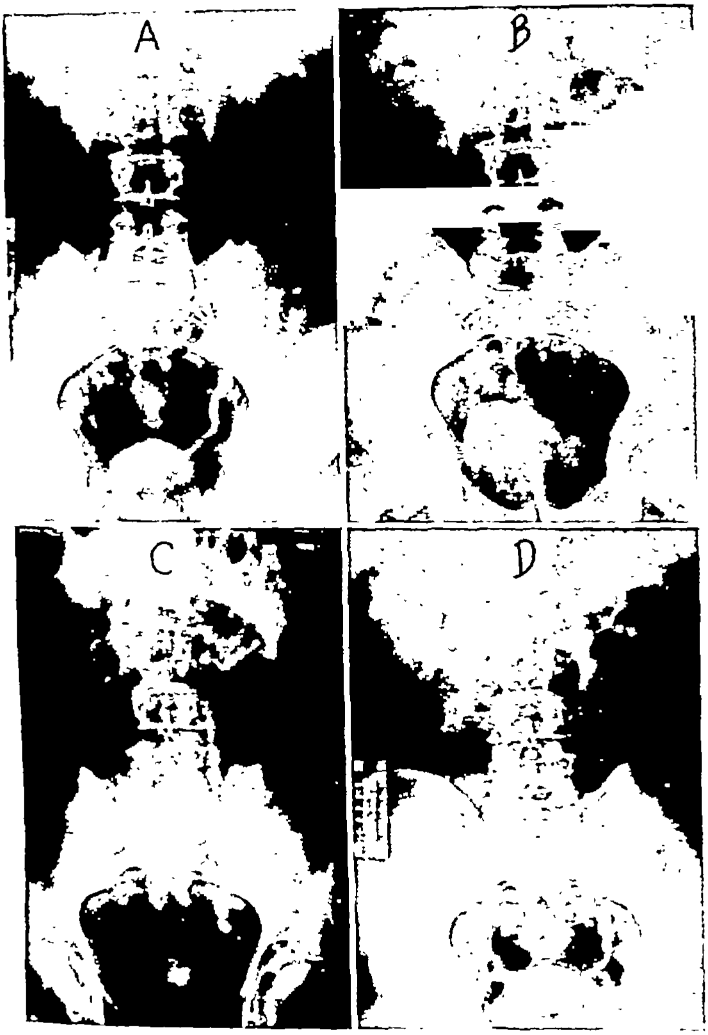

FIG. 2

The patient was not seen again until October 1949, fourteen months later, with a complaint of pain in the low abdomen referred to the penis. The blood pressure was 168/92. Urine was microscopically and chemically negative.

There was no further complaint until April 20, 1950, six months later, when the patient had a recurrent episode of the left abdominal colicky pain. Urine was microscopically and chemically normal. At cystoscopy, the right ureteral orifice was normal and spurting indigo carmine in strong concentration within 5 minutes of the intravenous injection. The left ureteral orifice could not be seen but a small, ureterocele-like bulging was evident in the corresponding region, revealing recurrent waves of a peristaltic nature. Excretory urograms showed a normal right pyelogram, but a left hydronephrosis and hydro-ureter, grade 2, with a ureterocele, grade 2 (fig. 2, *C*). Treatment consisted of transurethral slitting of the ureterocele and leaving a 9F ureteral catheter to the left kidney indwelling for one day.

Five months later, September 9, 1950, excretory urograms revealed segmental dilatation, grade 1, of the lower left ureter (fig. 2, *D*). The left kidney and upper ureter were now normal. The urine was microscopically and chemically negative. The blood pressure was 140/80.

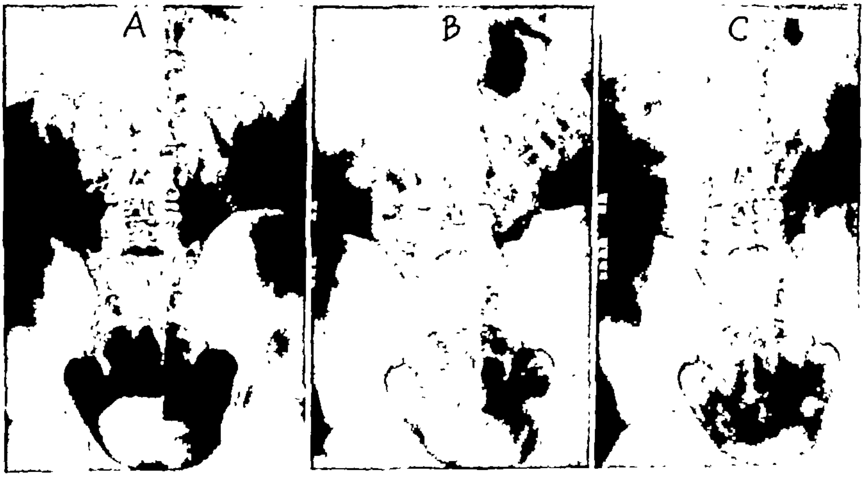

FIG. 3

This case illustrates injury to the left ureteral orifice by transurethral resection, with gradual stenosis, but without development of symptoms for 7 years. During the following 36 months, however, symptoms occurred in episodes at decreasing intervals. Finally, thorough urological survey revealed the condition threatening the left kidney, and surgical correction was effected.

Case 3. A white man, aged 55, was first seen July 7, 1947, with painless hematuria noted occasionally for 1 year and nocturia every 2 hours. The study revealed a papillary tumor about 5 cm. in diameter involving the region of the left half of the trigone and adjacent vesical neck, obscuring the left ureteral orifice. Excretory urograms showed normal anatomical and functional conditions of the right kidney, but left hydronephrosis and hydro-ureter, grade 2, with obstruction of the ureterovesical region (fig. 3, *A*).

Treatment on July 14, 1947, consisted of transurethral electroresection of the papillary tumor and thorough coagulation of its base. The left ureteral orifice was not identified. A 24 Foley 30 cc bag catheter was left indwelling. Pathological diagnosis was papillary transitional cell carcinoma of the bladder, grade 2.

Postoperative course was uneventful. The patient went home on the fifth postoperative day. Two weeks later, in the office, the urine contained a few white blood cells and a few red blood cells. At this time, excretory urograms revealed possible slight improvement of the left hydronephrosis (fig. 3, *B*).

For 10 months, the patient absented himself from our office and then came in response to a letter from us. He had no complaints. Cystoscopy at this time disclosed recurrent solid-type papillary tumor 3 cm. in diameter in the region of the left trigone. No indigo carmine could be seen coming from this region nor could the left ureteral orifice be identified. The dye was expressed normally from the right ureteral orifice.

May 11, 1948, a transurethral resection of the tumor with transurethral electrocoagulation of its base was again carried out. The ureter was not seen. The pathological diagnosis was the same. The patient went home on the fourth postoperative day and 2 weeks later the urine was clear. On December 11, 1948, excretory urograms with serial films up to 3 hours revealed no function of the left kidney (fig. 3, *C*).

The patient is now, 3 years later, without symptoms but presents himself for cystoscopy at 6 month intervals. Further recurrence of the tumor has not been seen. The blood pressure is 138/78 and the patient appears well.

This case illustrates the increased damage done to a ureteral orifice when both the resecting and coagulating currents are used extensively in its region. It also illustrates total loss of a kidney without the slightest symptom. If such kidneys are to be saved it must be at the time of the first operation, either by re-implantation of the ureter to the bladder in a remote location or by placing an indwelling ureteral catheter and performing periodic follow-up dilatations.

Case 4. A white male, aged 67, was first seen on July 11, 1949 in acute vesical retention. He had a history of a transurethral prostatic resection in 1948 by another urologist. For the past 6 months, he had had to catheterize himself daily. The bladder was distended and very hypotonic. Rectal examination disclosed a small prostate gland of benign consistency. Preoperative excretory urograms revealed normal upper urinary tract bilaterally and marked vesical hypotonia. (fig. 4, *A* and *B*). The right half of the bony pelvis was involved in Paget's disease.

July 13, 1949, with a 24F Stern-McCarthy resectoscope, a transurethral electroresection of 20 gm. of benign prostatic tissue was performed. The bladder was completely atonic and showed no trabeculation. The ureteral orifices were not mentioned in the cystoscopic or operative description. There was some slight postoperative shock, but the patient soon recovered following a single blood transfusion and was discharged home on the fourth postoperative day, afebrile, and wearing an indwelling urethral catheter.

The patient has been seen on an average of every 2 weeks since operation—that is, for the past 20 months—because of continued symptoms of dysuria. The urine has been intermittently almost clear or very cloudy with pus. The residual has varied from 0 to 500 cc. The report of a simple cystoscopy performed September 28, 1949, two months postoperatively, did not mention the ureteral orifices. The vesical neck was described as well resected. Notes on the chart indicate that, at times, a 26F sound passed readily but, at other times, with difficulty when the beak of the sound reached the region of the vesical neck. All symptoms of nocturia with urgency and dysuria were attributed to the hypotonic bladder and residual urine until December 27, 1950, eighteen months postoperatively, when cystoscopy was again performed.

At this examination, the bladder neck was described as bizarre, the posterior urethra as adequate, and the bladder as hypotonic. Neither ureteral orifice could be found. Intravenous indigo carmine did not help. A faint blue was visible in the trigonal region, but its origin could not be distinguished. Subsequent excretory urograms made March 21, 1951, with 30 cc 50 per cent neo-iopax and with serial films up to 3 hours, revealed totally absent function of the right kidney and left hydronephrosis and hydro-ureter, grade 3. The bladder was hypotonic (fig. 4, C).

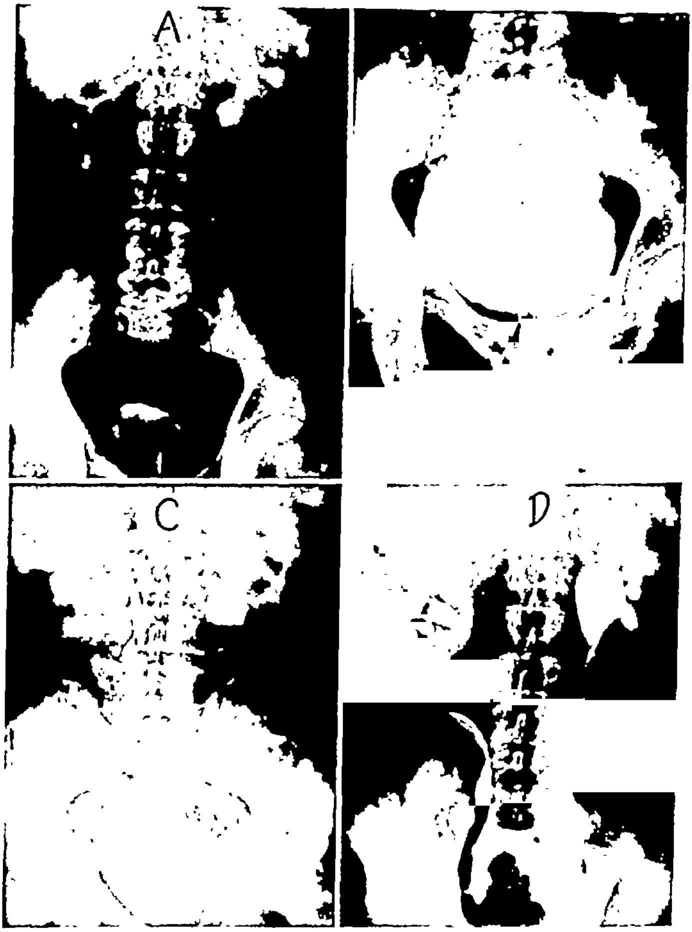

FIG. 4

Treatment consisted of cystoscopic dilatation of the left ureteral orifice and transurethral resection, uncovering the intramural portion of the right ureter.

A catheter left indwelling to the right kidney for 3 days revealed no function from this side (fig. 4, *D*).

This case illustrates bilateral ureteral injury by transurethral application of high frequency current. It probably represents a case of resection of the trigone. Barnes describes this and tells how to avoid it. The case also illustrates dramatically how much can be lost in urology by taking something for granted rather than investigating. Here the postoperative symptoms have been attributed to the known vesical hypotonia, while the renal function vanished from ureteral stenosis caused by transurethral electroresection.

Case 5. The patient was a white man, aged 80. No films are to be shown in this case, but the history and post-mortem findings tell the story. The patient entered the hospital January 8, 1951, and expired January 12, 1951. The complaint was fever for 2 days and bladder urgency and frequency for 4 years.

The past history revealed that, in 1947, he had had a transurethral electroresection of a large benign hypertrophied prostate gland by one of the most competent transurethral surgeons of America. He had gone home from the hospital on the tenth postoperative day and then became ill with fever which had lasted for 6 weeks. During this illness a cerebral thrombosis had occurred. The cause of the temperature, probably because of the absence of pain, had remained undiscovered. Since then, nocturia 3 to 4 times with dysuria and cloudy urine with occasional hematuria had been noted.

The physical findings revealed consolidation in the upper right lung field and marked pyuria. The patient expired on the fourth day after entering the hospital. An autopsy disclosed, in addition to the expected terminal pneumonia, a complete stenosis of the right ureter at the vesical junction and extensive right pyohydronephrosis. The prostate gland had been thoroughly resected. The pyonephrosis probably explained the post-transurethral resection febrile episode in 1947 as well as the continued urinary tract symptoms noted after the operation.

This case illustrates that ureteral injury by transurethral electroresection of the prostate gland can happen even in the most competent surgical hands.

DISCUSSION

The prophylaxis and treatment of the type of ureteral injury illustrated in these cases logically falls under three headings: preoperative, operative, and postoperative. An essential part of the preoperative prophylaxis of this injury should consist of excretory or retrograde pyelograms. Just prior to the beginning of the operation, the operator should identify cystoscopically each ureteral orifice, using intravenous indigo carmine if necessary. The right angle and the retrograde telescopes should be employed to discover the relationship of the trigone to the tissue that is to be resected. Note whether the trigone is foreshortened, normal, or elongated, and whether or not it is involved in a tumor mass, like a subtrigonal extension of prostatic carcinoma or hypertrophy. If a bladder tumor is to be resected, note its relationship to one or both ureteral orifices. As the resection proceeds, the mental image formed by the preoperative inspection must be kept in mind.

During the operation, when cutting in the neighborhood of a ureter, move the loop as rapidly as feasible and use as low a tube current as possible to effect severance of tissue. Do not cauterize at all unless a spurter is encountered, and then use point cauterization with as low a current as is effective. Positively refrain from placing or moving a loop back and forth in the neighborhood of a ureteral orifice when it is charged with a spark-gap current. If a ureteral orifice is included in the bladder tumor, it is best to do open surgery and re-implant the ureter away from the involved bladder. The tumor can then be resected through the cystotomy incision.

At the finish of the operation, identify again the ureteral orifices by inspection, if necessary with the intravenous use of indigo carmine. If a ureteral orifice cannot be seen and does not excrete indigo carmine when its mate does, it would be well to take one or two quick, but not too deep, loop tube current cuts in the region where the ureter should be. This should remove charred tissue and make it possible to identify the intramural ureter. If possible catheterize the ureter, even though it may be technically difficult, and leave the catheter indwelling for several days. In such a case, the kidney will require early and regular follow-up with excretory urography, and the ureteral orifice must be dilated repeatedly as indicated.

Traction on Foley catheters with large inflated balloons to control postoperative hemorrhage should be avoided lest irreparable damage be done to a ureter which might otherwise recover.

The operative record should include descriptions of the ureteral orifices as they appear both before surgery and after surgery. Make it part of routine procedure to include both.

During the postoperative hospitalization, if the temperature is elevated longer than 5 days, excretory urograms may reveal partial or complete obstruction of a ureter. It is essential to differentiate between bilateral ureteral injury and anuria from any cause, especially lower nephron nephrosis.

In the follow-up care of these patients, when prolonged postoperative pyuria or dysuria or occasional renal colic is present, regardless of the amount of the bladder residual, excretory urograms may decide the issue. Be suspicious if a sound impinges at the vesical neck, for this may mean excessive resection of the trigone and possibly associated injury of a ureteral orifice which may later stenose.

As part of the postoperative care in all cases, whether symptoms are present or not, excretory urographic studies would not only reveal how frequently this complication is occurring in our individual practices, but would also point the way to early treatment and thus forestall serious consequences.

Once stenosis has occurred, dilate the ureteral orifice early and as often as indicated. If stenosis is almost complete, enlarge the ureteral orifice by transurethral surgery, slit or resect superficially, and then insert a catheter. Be careful with the extent and depth of the resecting cut lest reflux up the ureter result or, if through the trigone, extravasation. In this event, it will be imperative to perform open surgery without delay to place a Penrose drain.

Should open surgery become necessary to save a kidney, ureteroneocystostomy should be carried out unless the old orifice can be satisfactorily opened and kept open through retrograde instrumentation from a ureterotomy incision and, later, cystoscopic dilatations. Finally, nephrectomy from severely infected hydronephrosis may be indicated.

SUMMARY

Five cases of ureteral injury from transurethral electroresection and coagulation have been reported. Points in the prophylaxis and treatment of the condition have been discussed and suggestions have been offered relative to future practice. It has been pointed out that the severe damage resulting to a kidney when its ureter has been so injured may pass completely without symptoms or may be the ultimate cause of uremic or infectious death.

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UROLOGIC COMPLICATIONS OF CANCER OF THE UTERINE CERVIX

EDWARD W. BEACH

It is a clinical maxim that some degree of pelvic ureteral occlusion is inevitable in many women afflicted by cervical cancer and treated with radiation. The medical profession has assumed that the x-ray and radium are responsible for such ureteral strictures and other complications, but a careful study of the last 24 patients referred to me has caused me to doubt this. Exactly what role, if any, does radiotherapy play in the development of such ureteral stenosis? What is the role of neoplastic parametrial spread with its attendant pother of inflammation, in the etiology of such ureteral occlusion?

Although every woman with cervical cancer is potentially a urologic patient, the experienced urologist is rarely intrigued by the actuality of urologic manifestations, because the latter usually have ominous import. More specifically, it is customary for the gynecologist to inaugurate and continue treatment of cervical cancer with no mind whatever paid the urinary tract. In fact, urologic talent is currently considered only a spare tire in the treatment ensemble and one reserved exclusively for a blowout. When such emergency occurs or the situation becomes desperate and vexatious urologic developments force belated consultation epitomized in those famous last words "For God's sake do something!" it is usually too late for anything but makeshift repair. Such malfeasance in management of cancer of the cervix uteri has, unfortunately, all but extinguished urologic interest in the treatment of this disease.

Moreover, many urologists have somehow acquired an impression that radiation therapy per se frequently causes stricture or atresia of the pelvic ureters. Theoretically and academically such a possibility is admissible, but the probability is remote and so is the incidence from a technical standpoint. Proof rests squarely on the proponent. Acceptance of the idea requires postmortem or factual evidence of which there is a remarkable dearth both in the literature and in my clinical experience. Ureteral stenosis of any degree is invariably accompanied by a palpable mass or increased denseness in the parametrium of the affected side or sides—whether neoplastic, inflammatory or organizing round-cell infiltration or some combination. A sound knowledge of cervical cancer with its infiltrative tendencies and concomitant inflammatory reaction plus a definitive understanding of radiotherapy seem the best antidote to such devil's wine.[1]

It is almost axiomatic that the close anatomic relationship between the uterine cervix and the adjacent urinary tract paves the way for urinary repercussions if cancer of any extent exists in the cervix, usually by spread from the primary focus or by inflammation, but sometimes by radiation therapy with the bladder as a selective target.

That cervical cancer deserves therefore a place on the top shelf of urologic interest is apparent in the following five facts:

Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 28, 1951.

[1] Vinum daemonum. Essays of Francis Bacon. Essay on Truth.

1) Cancer of the cervix comprises one of every four malignant tumors which afflict women. Breast cancer is first.

2) Sixty to eighty per cent of women so afflicted who succumb to this disease die of uremia contingent upon occlusion of the pelvic ureters.[2]

3) Direct spread into the juxtaposed bladder or urethra is not uncommon.

4) Surgical attempts to control such cancer still impose considerable injury on the ureter.

5) Postradiation or factitial cystitis—an entity often difficult to diagnose and to treat—is rampant because radiation therapy for control of such cancer is at the present being used more and more.

CANCER OF THE UTERINE CERVIX

This disease can exist in females of any age,[3] but it is most common among women older than 35, particularly in the married and parous.[4] It seldom afflicts the spinster and is less common among Jewish women.[5] The big age group from a diagnostic standpoint is around 48 years.

The vaginal portion of the cervix is covered by squamous epithelium with a sharp transition normally at the external os so that the endocervical canal is lined by a single layer of prismatic cells. Intrinsic glands therein have similar histologic architecture. These prismatic cells appear to constitute the nidus for so-called epidermoid cancer with its repertory of cellular morphology.[6]

Given proper instigation (the role of epithelial instability, heredity, sex, physiologic age, endocrine imbalance, infection and trauma all have supporters) these prismatic cells appear to undergo metaplasia and to become arranged into sheets or stratified pavement epithelium devoid of glandular elements, not unlike the epithelium over the portio vaginalis. Notable exceptions are 1) true cervical adenocarcinoma[7] (rare—only 3 to 5 per cent of cases) and 2) adenoacanthoma[8] with a relative admixture of both glandular and epithelial elements.

Classification of epidermoid cancer based upon cellular morphology, a task for the pathologist, depends on the predominant cell type. Multiform variations are usually present. Martzloff[9] divided this group into 1) the spinal cell type—the same as Broders'[10] grade 1 malignancy or "ripe" species, 2) the transition cell, or Broders' grade 2 malignancy still the "ripe" species and 3) the basal or fat spindle cell type—Broders' grade 3 and 4 malignancy—grade 3, the "middle ripe", and grade 4, "the unripe." In general, the anaplastic or dedifferentiated forms are most radiovulnerable, but they tend to spread early and they metastasize widely.

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[2] Cantril, Simeon T.: Radiation Therapy in the Management of Cancer of the Uterine Cervix. Springfield, Ill.: Charles C. Thomas, 1950, p. 23.

[3] Ackerman, Lauren V. and Juan A. del Regato: Cancer. Diagnosis, Treatment and Prognosis. St. Louis: The C. V. Mosby Co., 1947, pp. 852-854.

Heckel, G. P.: Pediatrics **5:** 924–929, 1950.

[4] Maliphant, R. G.: Brit. Med. J., **1:** 978–982, 1949.

[5] Weir, P. and C. C. Little: J. Heredity, **25:** 277–280, 1934.

Weiner, I., Burke, L. and Goldberger, M. A.: Am. J. Obst. & Gynec. **61:** 418–422, 1951.

Healy, W. P., and Twombly, G. H.: Am. J. Roentgenol., **49:** 522–523.

[6] Regaud, C. and Gricouroff, G.: Bull. Assoc. franç. p. l'étude du cancer, **22:** 285–296, 1933.

Regaud, C. Gricouroff, G., and Villela, E.: Bull. Assoc. franç. p. l'étude du cancer **22:** 668-677, 1933.

[7] Baclesse, F. and Fernandez-Colmeiro, J. M.: Bull. Assoc. franç. p. l'étude du cancer **30:** 118-128, 1942.

Ackerman, L. V. and del Regato, J. A.: Cancer. Diagnosis, Treatment and prognosis. St Louis: The C. V. Mosby Company, 1947, p. 859. (Incidence of 3.7 in 453 cases.)

[8] Randall, C. L.: Adenocarcinoma of the Uterus. In: Progress in Gynecology, vol. 11. Ed by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1950, p. 490.

Curtis, A. H. and Huffman, J. W.: A Textbook of Gynecology. Ed. 6, Philadelphia: W. B. Saunders Company, 1950, p. 338.

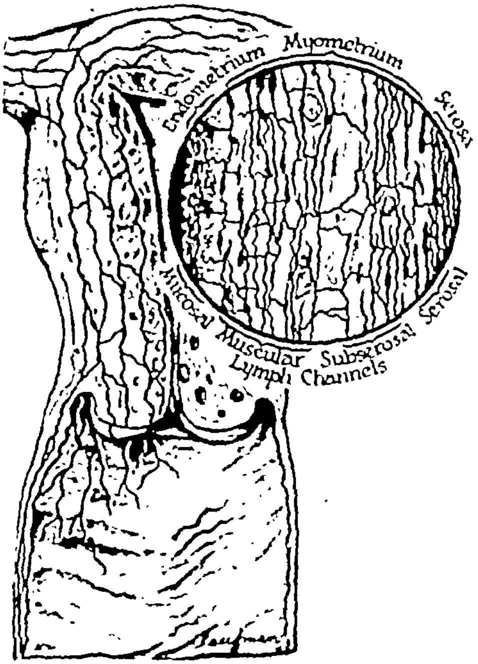

FIG. 1. Lymphatic drainage of uterus. Gross drawing: Large lymph channels. Longitudinal section: Microscopic endings of lymph system infiltrating walls of uterus. These may provide a means of metastasis.

Thanks to the pathologist's perspicacity, the nature of "noninvasive intraepithelial cancer"[11] of the cervix is now known. This condition has been called "basal cell hyperactivity", "carcinoma in situ,"[12] "beginnendes Karzinoma"[13] (by Schiller) and Bowen's disease.[14] It may antedate the frankly invasive clinical

[9] Martzloff, K. H.: Bull. Johns Hopkins Hosp., **34:** 141–149, 184–194, 1923.
Martzloff, K. H.: Bull. Johns Hopkins Hosp., **33:** 221–222, 1922.
Diseases of the cervix uteri. *In:* Practice of Surgery, by Lewis. Hagerstown, Md.: W. F. Prior Co., vol. 10, chap. 14, 1928.

[10] Broders, A. C.: Minnesota Med. **8:** 726–730, 1925.

[11] Te Linde, Richard W. The relation of "intra-epithelial carcinoma" to invasive cancer of the cervix. In: Progress in gynecology. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1946, pp. 349–361.

[12] Te Linde, Richard W. and Gerald A. Galvin: The present-day status of noninvasive cervical carcinoma. In: Progress in Gynecology, vol II. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1950, pp. 499–510.

[13] Schiller, Walter: Arch. f. Gynäk., **133:** 211–283, 1928.

[14] Bowen, John T.: J. Cutan. Dis., **30:** 241–255, 1912. Also, J. Cutan. Dis. **33:** 787–802, 1915.

entity for an indeterminate period—possibly a decade or even more.[15] Unfortunately the gross appearance of the cervix does not betray the presence of such a lesion.

Cervical cancer may spread in any direction by paracervical infiltration. Commonest is spread into the base of one or both broad ligaments. Extension upwards into endometrium or uterine wall is frequent (fig. 1). Distal infiltration of the portio vaginalis inclusive of the upper two thirds of the vagina is not rare. Later the lower third of the vagina may be invaded and this invasion is accompanied by inguinal adenopathy. Posterior extension toward the sacrum, rectum and sacral nerve roots may accrue and give rise to consonant subjective complaints.

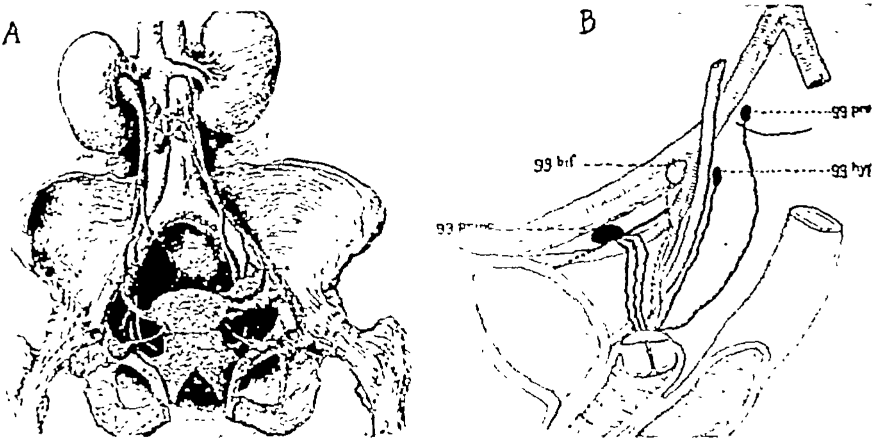

FIG. 2. *A*, lymphatic system of pelvic organs. Uterus, its appendages and vagina are covered by a rich network of lymphatic vessels surrounding uterus and vagina. *a* and *a′*, Lymph nodes at bifurcation of common iliac arteries. *b* and *b′*, Lumbar glands in pre-aortic chain. *c* and *c′*, Deep inguinal lymph nodes which may at times be involved by spread of carcinoma. (Through the courtesy of Cantril.[2])

B, Schematic view of initial lymph node relays of lymphatic supply of cervix. *gg. princ.*, Pre-ureteral chain (principal pathway). *gg. hyp.*, Hypogastric chain (post-ureteral). *gg. pro.*, Posterior chain leading to promontory. *gg. bif.*, Less frequent route leading to bifurcation of internal iliac. (Through the courtesy of Cantril.[2])

Lymphatic pathways are illustrated in figure 2. It is well to remember the dominant pre-ureteral trunk of lymphatic pathways into the broad ligaments which sponsors metastasis to pelvic glands from the obturator canal to the inferior iliosacral junction.

The League of Nations Committee[16] has adopted a workable classification based on extension proclivities:

Stage 1: Cancer confined entirely to the cervix.

Stage 2: Parametrium invaded on one or both sides. Some uterine motility retained. Lesion spread into corpus uteri and upper portion of vagina.

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[15] Te Linde, Richard W. and Gerald A. Galvin: The present-day status of noninvasive cervical carcinoma. In: Progress in Gynecology. vol. II. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1950, p. 506.

[16] League of Nations, Health Organization, Cancer Commission: Report submitted by the Radiological Sub-Commission, Geneva, League of Nations Publications, 1929, 82 pp.

Heyman, J.: Atlas illustrating the division of cancer of the uterine cervix into four stages. League of Nations Health Organization (Inquiry into the results of radiotherapy in cancer of the uterus). 1938, unnumbered pages.

Stage 3: Infiltration extended through parametrium to pelvic wall—isolated masses palpable on pelvic wall. Lower third of vagina involved.

Stage 4: Cancer involves bladder or rectum with spread outside the pelvis to other viscera.

Because infection, cellulitis and inflammatory induration invariably accompany cancer spread, proper evaluation sometimes perplexes the most experienced.

Diagnosis. Microscopic study of segregated scrapings from the cervix and uterus, using Papanicolaou or similar technique is sometimes helpful, but biopsy is essential. Cytologic and clinical study of the primary lesion and of extracervical spread conditions both treatment and prognosis. Symptoms vary. Abnormal or postmenopausal bleeding should arouse suspicion. Contemporary physicians must be mindful that abuse of estrogenic therapy during menopause is now common.

Treatment. The field of therapy has laid somewhat fallow for the last few years. This may presage a bumper crop of new developments.

In the surgical era all hope hinged upon the radical Wertheim[17]—the most formidable of all gynecological procedures—with a high mortality rate and a frightful bladder and ureteral morbidity especially in the hands of the inexperienced. The bladder suffers injury in about 17 per cent of cases; vesicovaginal fistulas occur in about 7 per cent.[18] Even in expert hands, the ureters are injured in 7 to 10 per cent[19] of cases; often the blood supply to the ureters is impaired and sloughing results. In 28 years of practice I have treated 14 such injuries, most of them resulting in ureterovaginal fistula, following the Wertheim procedure. We have the Wertheim operation to thank for much of what we know about cervical cancer—learned at the operating table and from pathologic specimens. The Martzloff modification[20] is now more commonly used.

Most clinics now take a dim view of surgical treatment alone, save in very early and selected instances. Granted that the lesion is "cancer in situ", what surgical procedure should be undertaken? Trachelectomy? Simple hysterectomy? Hysterectomy plus adnexectomy? The more radical Wertheim? Who knows? Anatomic studies of this entity have taught the necessity of removing an ample cuff of tissue about the limits of the portio vaginalis in these cases.[21]

Many clinics in this country now depend solely upon x-ray and radium to control cervical cancer. Those that have good radiotherapy departments put out an imposing array of statistics in support of their method. The gist of such statistical tables is that if treated early, possibly 8 of 10 cervical cancers may be controlled by radiotherapy and that later when one or both parametria are invaded, perhaps 1 of 3 may be so controlled, depending on the extent of invasion, the cellular morphology and who presents the statistics. It offers the additional advantage that the patient is ambulatory throughout. Clearly radiotherapy is most favored in the current approach. However, because the metastatic lesions of some tumors are radiation-resistant, removal of the pelvic lymph glands on both sides is advocated after preliminary and intensive radiation. Taussig[22] uses such a procedure, without hysterectomy, and Nathanson[23] also uses it, with extraperitoneal exposure, in certain cases. Recently Meigs[24] has coupled the radical Wertheim operation with Taussig's gland resection in selected cases.

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[17] Wertheim, E.: Am. J. Obst., **66:** 169–232, 1912.
Bonney, V.: Am. J. Obst. & Gynec., **30:** 815–830, 1935.
Meigs, J. V.: Am. J. Obst. & Gynec., **49:** 542–549, 1945.
Meigs, J. V.: In: *Progress in Gynecology*, vol. II. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1950, pp. 540–561.

[18] Weibel, W.: Arch. f. Gynäk., **135:** 1–57, 1928
Weibel, W.: Wein. Klin. Wchnschr., **38:** 716–717, 1925.
Wharton, L. R.: Gynecology. With a Section on Female Urology. Ed. 2, Philadelphia: W. B. Saunders Company, 1947, p. 501.

[19] Wharton, Lawrence R.: Gynecology. With a Section on Female Urology. Ed. 2, Philadelphia: W. B. Saunders Company, 1947, p. 495.

[20] Martzloff, Karl H.: Bull. Johns Hopkins Hosp., **34:** 141–149; 184–191, 1923.

[21] Foote, F. W., Jr. and Stewart, F. W.: Cancer **1:** 431–440, 1948.

While time has proved the value of radiation (in terms of 5 year control) there is as yet no unanimity as to dosage, modalities, application or sequence. Multifacets in the clinical picture stemming from the cellular morphology, conformation of the primary lesion, the presence of infection or cellulitis, the route and degree of extension, the pelvic pattern and the general condition of the patient all preclude standardized technique. Nor can radiation be used empirically or with a slide rule. Radiation must be tailored to the individual by the skilled radiologist in an effort to eradicate the cancer cells and yet preserve the integrity of normal surrounding tissues. The patients who are the subject of the discussion to follow underwent a high voltage ("soft ray") barrage through four skin portals (2A and 2P) using 8.000 to 10,000 r, and in suitable cases 3,000 to 4,000 r was given by vaginal cone. Radium element properly screened was used after the Stockholm[25] technique, about 3,000 mg. hr. in the uterine corpus and 3,000 to 3,500 mg. hr. to the cervix and vaginal fornices. Alterations and modifications governed by the attendant circumstances were frequent.

UROLOGIC COMPLICATIONS

The relevant clinical data from my 24 cases will be presented in the following general discussion of the urologic complications in radiation therapy of cancer of the cervix.

The pelvic ureter. Figures 3 so 6 provide anatomic reconnoiterer. Of esoteric interest is the parametrial ureter which passes forward to the cervix and then

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[22] Taussig, F. J.: Am. J. Obst. & Gynec., 45: 733–748, 1943.
Leveuf, J. and Godard, H.: J. de chir. 43: 177–187, 1934.

[23] Nathanson, I. T.: Extraperitoneal iliac lymphadenectomy in the treatment of cancer of the cervix. In: Progress in Gynecology. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1946, pp. 388–394.

[24] Meigs, Joe V.: Radical hysterectomy for cancer of the cervix with bilateral pelvic lymphadenectomy (the so-called Wertheim operation). In: Progress in Gynecology, vol. II. Ed. by Joe V. Meigs and Somers H. Sturgis. New York: Grune & Stratton, 1950, p. 541.

[25] Heyman, J., Reuterwall, O., and Benner, S.: Acta radiol. 22: 11–98, 1941.
Forssell, G.: Acta radiol., 28: 417–432, 1947.
Forssell, G.: Hygeia, vol. 76, 1914.
Forssell, G.: Fortschr. der a. d. Geb. d. Röntgenstrahlen, 25: 142–149, 1917.
League of Nations, Health Organization, Cancer Commission: Report submitted by the Radiological Sub-Commission. Geneva, League of Nations Publications, 1929, 83 pp.
Heyman, J.: 20: 85–91, 1947.

downward and medially to the trigone. Of greatest urologic import is that ureteral segment where "water passes under a bridge" (ureter crossed by the uterine artery) which is almost opposite the internal os and about 1½ cm. lateral to the cervix and that downward ureteral continuation ensheathed by the veins of the vesicovaginal plexus which lies about 1 cm. above the lateral vaginal fornix. The most distal ureteral portion, about 1½ cm. long, *lying close to the vaginal* wall, is also implicated by the cervical cancer.

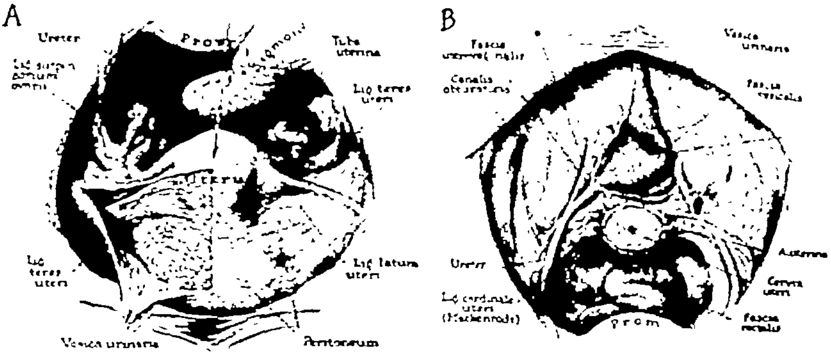

FIG. 3. *A*, cross-section of female pelvis, showing basal structure of broad ligament, ligamentous supports of bladder and uterus, and fascial coats of pelvic organs.
B, female pelvis, anterior view. Subperitoneal tissue of broad ligament, urinary bladder and uterus. Uterus is retracted from its normal anteverted position and peritoneum has been pulled back to show body of uterus, broad ligament and superior surface of bladder.

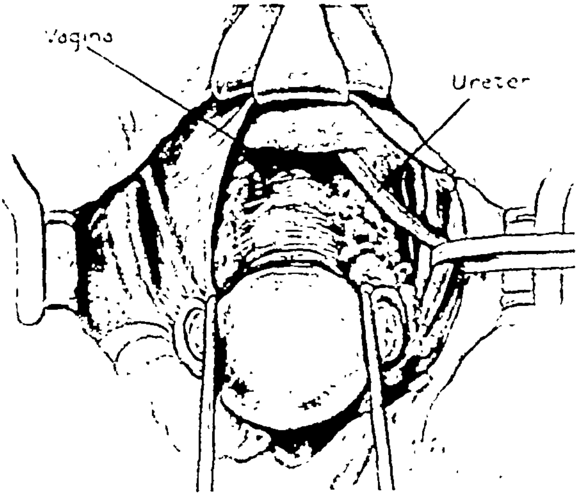

FIG. 4. Female pelvis, anterior superior view. Right ureter has been freed completely from its bed from 3 cm. below pelvic brim to trigone. Note proximity of parametria and pelvic lymph nodes to uterus. (*Through courtesy of* G. H. Twombly: Technique of radical hysterectomy for carcinoma of cervix. Cancer, 3: 975-991 [Nov.] 1950.)

The terminal segment of pelvic ureter, some 7 to 8 cm. in length, is not only in close anatomic apposition to the cervix, but is also served by *much the same* lymph and blood vessels. Any morbid change in the cervix should therefore be reflected in some degree or have reciprocative amplification in the abutting ureter, conditioned by the character of the lesion, from initial hyperemia to compression or angulation of the duct because of parametrial extension.

The commonest point of ureteral occlusion in parametrial spread is where the duct is crossed by the uterine artery (fig. 7); i.e. adjacent to the internal os and about 5 to 6 cm. up from the ureteral meatus. Twelve patients (all seen in the "supplicatory stage"—stages 3 and 4) had variable degree of occlusion at this point on one or both sides. In 5, nephrectomy was necessary because of unilateral occlusion with sepsis and because great debilitation precluded other measures for relief. In another case with uremia, since only half a kidney remained, a quick ureterocutaneous groin fistula was established. In 3 other cases the vaginal or most distal ureteral segment was obstructed unilaterally. In 2, a stone was impacted in this pathologically narrowed portion and in another, ureteral occlusion was caused by neoplastic impingement near the anterior vaginal wall.

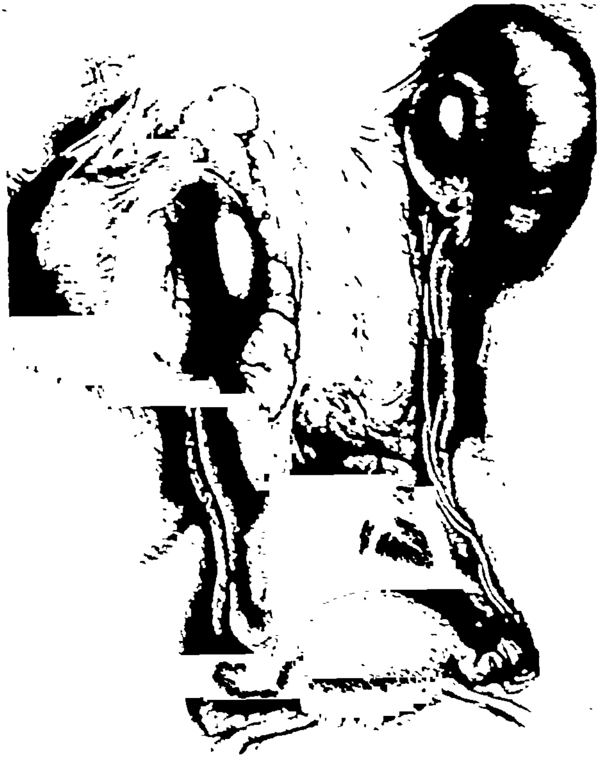

FIG. 5. Bilateral hydro-ureter due to obstruction arising from spread of cancer of cervix. (Through the courtesy of Cantril.[2])

In exact discernment of the presence and degree of ureteral occlusion, both retrograde (if possible) and excretory roentgenologic studies are necessary. The fact that a catheter can be passed up the ureter does not mean that the ureter is not partially occluded by segmental narrowing, extra-ureteric pressure or edema of the ureteral wall. It is quite common to thread a catheter through such an area of involvement initially and never again be successful in such endeavor.

Indwelling catheters were poorly tolerated in these cases. Interval ureteral dilatations were not too helpful.

The cause of ureteral occlusion in these cases was invariably a mass or some degree of induration in the base of the broad ligament—whether neoplastic or inflammatory or both, only clinical experience and observation could determine. In none of this limited group could radiotherapy be incriminated for the ureteral stenosis. In fact, in two cases partial bilateral ureteral occlusion and subjective symptoms were relieved considerably by a second course of radiation therapy.

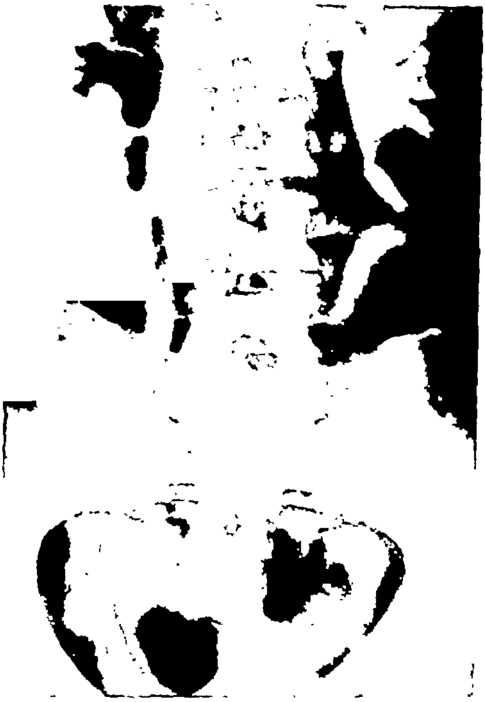

FIG. 6. Early bilateral ureteral backpressure due to cancer of uterine cervix. Patient was a young woman. Conditions suitable for ureteral transplantation.

If the condition is advanced, seldom is reconstructive surgery advisable. Bilateral ureteral occlusion usually has dire prognostic connotation and hence nephrostomy or a shift of the ureter to the intestine or the contralateral structure has limited application from a practical standpoint in view of the psychology, general condition and life expectancy of such patients.

The bladder. If cervical cancer spreads downward along the anterior vaginal wall, seldom does the bladder escape unscathed. Such extension—usually a forerunner of vesical involvement—can sometimes be palpated long before urinary symptoms are manifest. Excellent studies[26] depicting cystoscopic changes and successive steps in the development of such bladder lesions which range from early trigonal asymmetry or distortion at the base through submucosal petechiasis and edema to actual nodule formation with ulceration and bleeding have been made and need no reiteration here.

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[26] Aman-Jean, F.: Bull. Assoc. franç. p. l'étude du cancer 22: 556–559, 1933.
Graves, Roger C., Kickham, C. J. E. and Nathanson, I. T. Surg., Obst. & Gynec. 63: 785–793, 1936.

Among the 24 cases there were 2 vesicovaginal fistulae and 1 rectovesical fistula—obviously late and hopeless sequelae.

Post-radiation cystitis: From the practical standpoint there are two types—an early and a late or delayed type. Much work has been done by Dean,[27] Colby[28] and others[29-30] on this subject.

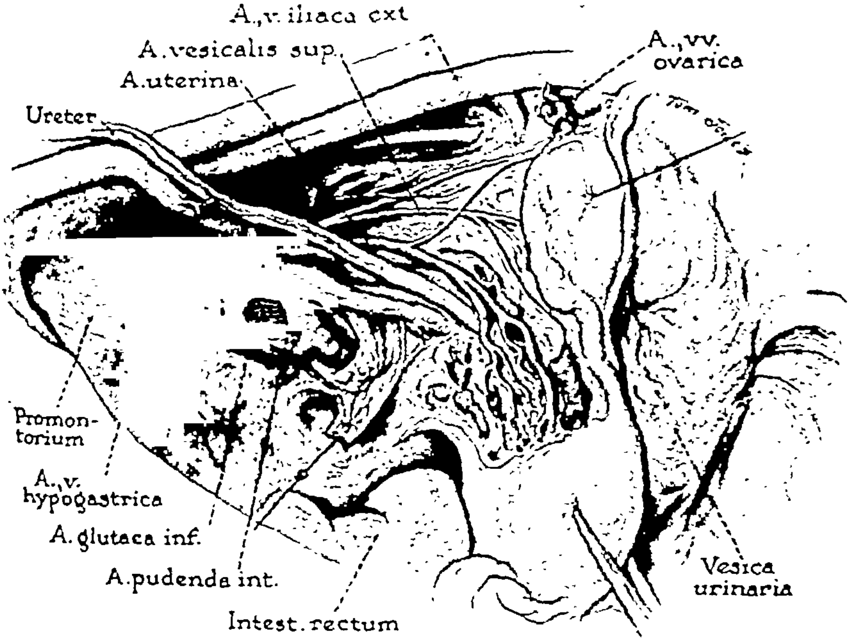

FIG. 7. Principal arteries and veins supplying organs of female pelvis. Uterine artery has been further exposed by partial removal of accompanying veins. All remaining structures still lie in positions they held prior to dissection. Note point at which ureter is crossed by uterine artery, common point of ureteral occlusion in cases in which parametrial spread has occurred.

The early type is a vasodilatation phenomenon and represents a specific response to radiation. It comes along 28 to 30 days astern of treatment. Subjective symptoms are rarely severe and usually clear quickly. If deep therapy alone is used, generalized cystitis is discovered with the cystoscope. If such reaction depends solely upon intracavitary use of radium element, areal distribution over the bladder base at certain points of maximal concentration is apparent cystoscopically. Every urologist who collaborates closely with the radiologist is familiar with such changes.

The delayed type of factitional cystitis is signalized by its tardy appearance after radiation. It seldom develops before a year has elapsed and may be delayed for as long as 10 to 12 years after radiotherapy. Average appearance time is given as 2½ years. This type of bladder lesion constitutes a *trophic change* predicated upon an obliterative endarteritis. It is characterized by sloughing of the bladder wall or trigone in variable degree. The slough may be so deep and extensive that a fistula forms. Subjective symptoms are often distressing and the healing of such a lesion is very slow. Usually the cervical cancer is well controlled before these bladder lesions become apparent.

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[27] Dean, A. L. Jr.: J. A. M. A. 89: 1121-1123, 1927. Also J. Urol. 29: 559-570, 1933.
Dean, A. L. Jr. and Slaughter, D. P.: J. Urol., 46: 917-924, 1941.
[28] Colby, F. H.: New Eng. J. Med., 209: 231, 1933.
[29] Everett, H. S.: Am. J. Obst. & Gynec. 38: 889-906, 1939.
[30] Newell, Q. U. and Crossen, H. S.: Surg., Gynec. & Obst., 60: 763-768, 1935.

There were 5 instances of delayed postradiation cystitis in my series. The youngest woman was 37 and the oldest 66 years of age. The earliest appearance of this trophic lesion was 17 months after radiation and the latest, 35 months thereafter. Each of these women had had at least 5,000 mg. hr. of intracavitary radium and none more than 6,200 mg. hr. These trophic bladder lesions were invariably multiple and comprised a number of moderate sized, shallow, irregular ulcers, usually *retrotrigonal and toward the left lateral wall*. These ulcers had a linear distribution, the edges were somewhat motheaten and the floor was covered with grayish yellow necrotic material. They were surrounded by an injected areola. Dysuria was prominent, especially frequency and burning. Hematuria was always an outstanding symptom.

The cystoscopic appearance of such lesions is quite misleading and diagnosis necessitates careful cytological study of several biopsy specimens. It is most important to avoid subsequent radiation—if no cancer cells exist. Diagnosis is sometimes a problem even for the skilled pathologist in these instances, as the following case demonstrates: One of my patients had suffered a transitional cell cervical cancer which had been treated by radiation and 5,000 mg. hr. of intracavitary radium (well screened). This cancer was well controlled clinically. About 18 months after radiotherapy, a group of trophic bladder ulcers appeared, accompanied by the usual subjective and objective symptoms. A series of 3 or 4 biopsy specimens was obtained from the most suspicious areas. The pathologist, who had had 38 years of experience, stated that the lesion was a transitional cell bladder tumor with cellular morphology much like that of the cervical cancer which he had previously studied. Because of the patient's history, we were dubious and took several more biopsy specimens. Again the same pathological diagnosis. Meantime the patient grew restless and because of her urinary distress, enplaned for the Mayo Clinic. Dr. Edward N. Cook of the Clinic took 18 or 20 biopsy specimens before he could be certain that there were no cancer cells. Under his care the patient's symptoms were shortly relieved and the ulcers healed in approximately 6 months.

The trophic ulcers I treated healed very slowly and usually required 6 to 10 months. Therapy, empirical or otherwise, did not seem to hasten healing. For the hyperacute cases of dysuria, continuous bladder irrigations with dilute silver solution (1:3,000) was most helpful. Later, hydrostatic bladder dilatations followed by oily balsamic instillations gave some relief. In none of these cases did fistulae develop.

The urethra. As the cervical cancer spreads downward along the anterior vaginal wall, in late stages, the urethra may be impinged upon by the neoplastic mass surrounding it or its wall may be invaded directly by the cancer. I had one such case; retention developed and catheterization was very difficult and painful because of the narrowed and compressed urethral lumen. A permanent cystostomy was made to relieve symptoms.

Adjuvant treatment. Competent management of cervical cancer necessitates inquiry into the urologic status of these patients both initially and at appropriate intervals thereafter. If this is done and attention is thereby focused on the pelvic ureters before they become hopelessly fouled in this disease, the patient can be given much better care. For many of these unfortunate women, early ureterosigmoidostomy would be a blessing, if partial bilateral ureteral occlusion is worsening clinically. In another limited group, when the bladder is threatened by advancing spread of the cancer, but has not yet been involved, total cystectomy with uretero-intestinal transplantation might constitute a wise choice of treatment. Prevention of trophic bladder lesions is difficult in the absence of a reliable gauge for predetermining unusual individual susceptibility to radium, but better screening and more care in placement would help.

SUMMARY

This article hopes to rekindle interest by stressing urologic repercussions in cervical cancer and to dispel some common fallacies by review of basic knowledge. It recalls certain factors pertinent to cervical cancer in its bearing on the adjacent urinary tract. It brings up the question whether radiotherapy per se induces ureteral stenosis in these cases and presents evidence that extension of the disease is the more likely cause. In these 12 cases of ureteral obstruction it was the only cause. It pleads for a preliminary and detailed urologic survey before any treatment of the cancer is begun so that early or unsuspected lesions of the urinary tract may be discovered and expeditiously cared for. It urges closer liason between the urologist, the gynecologist and the radiologist to the end of efficient management. The close anatomical relationship of the uterine cervix and the ureters obligates every urologist to actively crusade against current neglect of the urinary tract in the treatment of cancer of the cervix. Supplicatory consultations are too common and are a sad commentary on scientific management of this disease.

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THE USE OF SEGMENTS OF SMALL INTESTINE AS URETERS

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The use of a segment of small intestine to replace a strictured portion of one ureter was reported by Nissen in 1940.[1] The operation was clinically successful, but no postoperative studies were reported. To date no experimental work has substantiated the feasibility of this procedure. Reports of previous experiments indicate that when all of the urine is emptied into the small bowel, or into a segment of the small bowel which is not exteriorized, the animals die from renal insufficiency.[2–5] Evidence has been advanced to show that these deaths are due to absorption of urinary products.[6–9] Groto in 1918 was inclined to attribute the death of these animals to rentention rather than to the absorption of urinary products.[10] Later writers have emphasized the importance of obstruction at the site of uretero-intestinal anastomosis as a cause of renal insufficiency.[11–14]

Mersheimer and his co-workers, at New York Medical College and Flower and Fifth Avenue Hospitals, reported anastomosis of both ureters to a 10 cm. isolated segment of small intestine in a dog, with exteriorization of the end of the loop.[15] The dog, sacrificed at 18 months, showed no kidney infection but did show some dilatation of the ureters. The enterostomy stoma was reported to be normal. The technique of caring for the stoma was not reported.

Matsumoto in his first experiment partially isolated 35 cm. segments of small bowel at different levels in the intestine in an effort to overcome the ascending infection and to study the effects of absorption.[16] This operation was carried out in two stages in 107 dogs. He found it impossible to prevent ascending infection. The implantation of both ureters resulted in the death of the animals in from 7 to 12 days. When the upper part of the small intestine was used the nonprotein nitrogen increased more rapidly, but the period of survival was not always correspondingly affected. He did not believe that the elevated nonprotein nitrogen was due to the absorption of urine.

Read at annual meeting, American Urological Association, Chicago Ill., May 22, 1951.

[1] Nissen, R.: J. Internat. Coll. Surg., **3:** 99–102, 1940.

[2] Steinke, C. R.: Univ. Penn. Med. Bull., **22:** 22–110, 1909.

[3] Baird, J. S., Scott, R. S. and Spencer, R. D.: Surg. Gynec. & Obst., **24:** 482–484, 1917.

[4] Hinman, F. and Belt, A. E.: J.A.M.A., **79:** 1917–1924, 1922.

[5] Bollman, J. L. and Mann, F. C.: Proc. Soc. Exper. Biol. & Med., **24:** 923–924, 1927.

[6] Hartman, F. W.: J. Exper. Med., **58:** 649–662, 1933.

[7] Ormond, J. K.: J. Urol., **29:** 15–28, 1933.

[8] Cecil, A. B. and Cummings, R.: J. Urol., **2:** 469–480, 1918.

[9] Boyce, W. H.: J. Urol., **65:** 246–261, 1951.

[10] Groto, K.: J. Exper. Med., **27:** 449–458, 1918.

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In his second report on 102 dogs he used 35 cm. segments of bowel which were completely excluded from the intestine and the distal end exteriorized.[17] When both ureters were anastomosed to this isolated loop there was a rise in nonprotein nitrogen which returned to normal in about 7 days. All of the animals lost their appetite and all died in 30 to 40 days. He attributed death to infection and maceration of the skin around the enterostomies, and to malnutrition. No mention was made of urinary tract infection in this second group.

In our study we have used 20 cm. isolated segments of terminal ileum to replace one or both ureters. The diet was uniform and water was constantly available. Food was withheld for 24 hours before surgery. Intravenous sodium nembutal 0.2 cc per pound of body weight was used for anesthesia in all cases. A total of 16 dogs were used in this experiment; two were rejected on account of disease, two were used as controls and twelve were operated upon. The operation consisted of isolating a 20 cm. segment of terminal ileum, taken about 25 cm. from the cecum. The continuity of the bowel was re-established by end to end anastomosis with two layers of interrupted No. 60 cotton. The isolated loop was irrigated with 500 cc of 1 per cent suspension of sulfathiozole in sterile normal saline. No other measures were used to prevent urinary tract infection.

The proximal end of the isolated loop was closed; the distal end was carried through the root of the mesocolon and the left broad ligament, and anastomosed to the back of the urinary bladder end to side with two layers of interrupted cotton. When both ureters were replaced, the segment was anastomosed at the hilus of the left kidney and then passed through the root of mesentery to the lower pole of the right kidney where it was anastomosed to a longer segment of ureter. The bowel ureter was then carried down on the right side and anastomosed to the bladder.

The uretero-intestinal anastomosis was carried out by dividing the ureter about 3 or 4 cm. from the kidney hilus and splitting the end for a distance of 1 cm. A suture with double needles was then passed through the corners of the split ureter. These traction sutures were used to draw and anchor the end of the ureter within the lumen of the bowel. This technique was used with both cotton and catgut. With both there were complications which will be described later.

We believe that a mucosa to mucosa anastomosis such as that described by Nesbit would be better, but in these dogs the ureter was so small right up to the hilus of the kidney that we had neither the skill nor the courage to attempt it.[18]*

In all of the operated dogs the kidneys were approximately equal in size and consistency at the time of surgery. Twenty two surgical procedures were carried out on the twelve dogs. Three of the dogs died. Dog No. 4 died 7 weeks after the left ureter had been replaced by a segment of small intestine. Autopsy showed a volvulus of the remainder of the small bowel around the isolated segment with resulting strangulation, perforation and peritonitis. The other two deaths were due to renal insufficiency caused by obstruction at the site of uretero-intestinal anastomosis after the opposite kidney had been removed.

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* Since completing this work we have succeeded in making a mucosal anastomosis between the left ureter and bowel at the kidney hilus and removing the right kidney at one operation. This dog appears normal after 3 months.

[17] Idem. Arch. f. jap. Chir., **15:** 515-557, 1938.

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Early in our study we observed that not all dogs are equally suitable for study. Some that are apparently normal will show an erratic curve of the nonprotein nitrogen, even when all controllable conditions are held uniform. In one instance, where the animal had only a 20 cm. segment of small bowel excised and the intestine re-established by end to end anastomosis, 10 determinations of the nonprotein nitrogen were made in the 32 weeks following surgery and only on three occasions did the reading fall within the average normal range. However, all of the tests gave readings well within the limits of values found in normal dogs by Haden and Orr.[19]

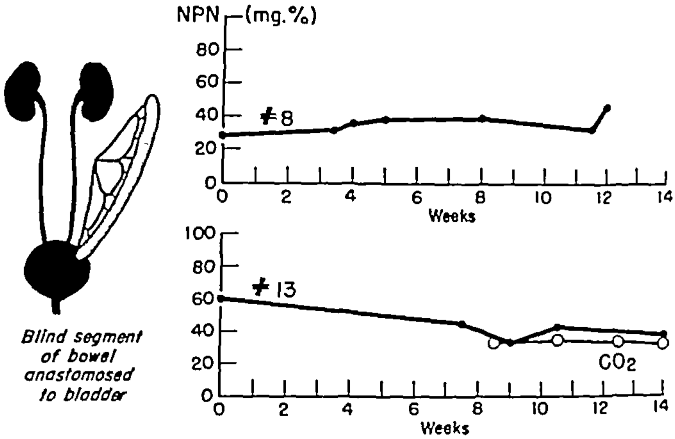

FIG. 1. Showing that an isolated loop of small bowel connected with bladder to permit absorption, but with no interference with normal transport of urine, has no demonstrable effect on nonprotein nitrogen or in dog 13 also on plasma CO_2.

Since curves with wide variations are difficult to interpret we believe that each dog should have several preoperative determinations and only those animals selected for surgery that show relatively uniform and consistent tests.

In 1 dog both ureters were ligated in order to determine how long the animal would survive under the conditions of this experiment. Figure 1 shows that the animal died in 90 hours; at the end of 72 hours the nonprotein nitrogen was 262.1 mg. per cent.

In 2 dogs a 20 cm. segment of small intestine was isolated, closed at its proximal end and the distal end anastomosed to the urinary bladder. This procedure permitted the contact of urine with the mucosa of the bowel but did not interfere in any way with the normal transport of urine from the kidneys to the bladder. Figure 1 shows that there was no significant elevation of the nonprotein nitrogen or plasma chloride levels. Except for the length of bowel segment used, this part of the experiment corresponds to that reported by Hartman.[5]

In 6 dogs a 20 cm. segment of small intestine was used to replace the left ureter (fig. 2).

[19] Haden, R. L. and Orr, T. G.: J. Biol. Chem., 65: 479-481, 1925.

All of these dogs showed an initial rise in the nonprotein nitrogen to 70 to 80 mg. per cent and then a decline. Half of these dogs returned to the preoperative level within 6 weeks. In the remainder the nonprotein nitrogen was elevated 25 per cent to 30 per cent above the preoperative level. This is contrary to the findings of some investigators who report only a very transient elevation of nonprotein nitrogen when the uretero-intestinal anastomosis is done only on one side.[4, 5, 16] This result may be due to a poor selection of animals for this part of the experiment.

In dog No. 1 twenty-two nonprotein nitrogen determinations were made in the course of 1 year. The nonprotein nitrogen level was rather erratic. Biopsies were taken from the bladder, the normal bowel, the bowel used as ureter and of both kidneys at the end of 3 months.

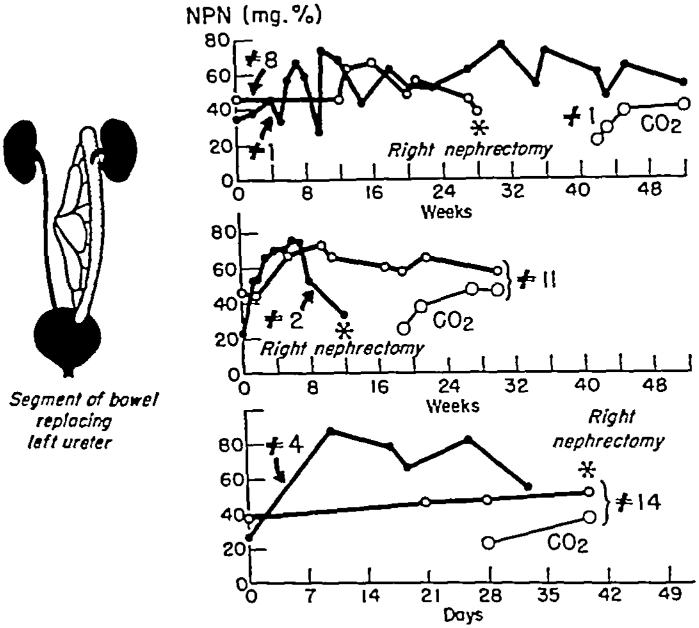

FIG. 2. Showing effect in 6 dogs of substituting an isolated segment of small bowel for left ureter.

The bladder showed mild cystitis. The bowel used as ureter showed no change from normal bowel except contraction. The left kidney was smaller and firmer in consistency than the unoperated right kidney and there were several small flat, depressed scars on its surface. At the end of 1 year the dog was sacrificed and the tissues examined. The bowel ureter was tightly contracted and contained considerable mucus. Microscopically it appeared like normal bowel showing no change except contraction. The goblet cells were just as numerous and as active as in the normal bowel. Figure 3 shows the relative size of the normal bowel, normal ureter and bowel used as ureter.

There was slight tendency for the epithelium of the bladder mucosa to grow over the mucosa of the bowel at the site of anastomosis (fig. 4). The bladder epithelium did not tend to penetrate the glands and the growth was too slow to be of clinical significance.

There was no contraction at the site of vesico-intestinal anastomosis. There was some constriction at the site of the uretero-intestinal anastomosis but the lumen was sufficient for the free passage of urine.

The left kidney weighed 20.4 gm. and appeared smaller and firmer than at 3 months. The right kidney weighed 34 gm. and appeared normal. The left kidney was scarred and on section showed a patchy pyelonephritis. The pelvis was thickened and the infective process extended through numerous areas of the medulla and to a lesser extent through the cortex. There was still about 60 per cent of essentially normal tissue in the left kidney. The right kidney appeared normal.

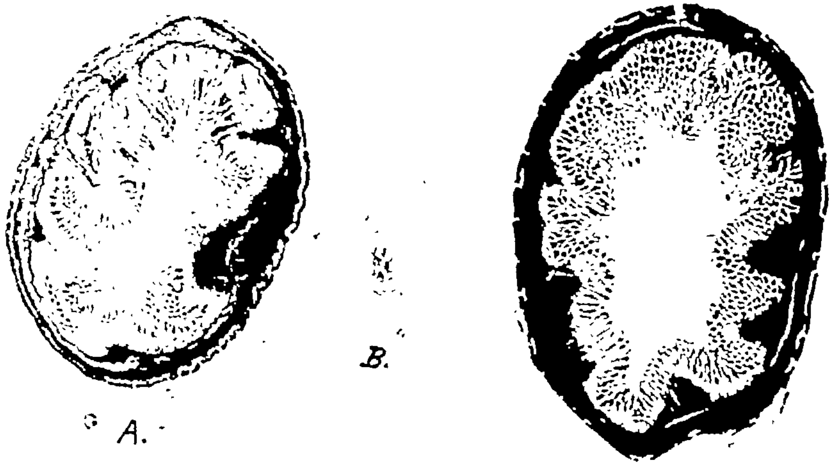

FIG. 3. *A*, bowel used as ureter for 1 year. *B*, normal ureter. *C*, normal bowel. No change in bowel except contraction.

In three of the 6 dogs in which the left ureter was replaced by an isolated segment of small bowel the opposite normal kidney was later removed. Two of these dogs died of renal insufficiency due to complete obstruction at the uretero-intestinal anastomosis.

Dog No. 2 had a right nephrectomy 84 days after replacement of the left ureter by a segment of bowel. There was an initial rise in the nonprotein nitrogen which returned to normal in 14 days. The animal remained clinically well but showed a gradual rise in the nonprotein nitrogen to a level of 90.3 mg. per cent on the eightieth postoperative day. Eleven days later the animal became listless, anorexia and diarrhea developed and died on the ninety-fifth postoperative day, having been clinically ill only 4 days. At autopsy the remaining left kidney showed hydronephrosis and a complete obstruction at the uretero-intestinal anastomosis. The lumen at the site of anastomosis had gradually contracted and then had suddenly become plugged by a calcareous deposit which had formed on a cotton suture in this area. There was evidence of pyelonephritis in this kidney. The enterovesical anastomosis showed smooth healing with no contraction.

Following this experience we used 0000 chromic catgut to make the ureteral anastomosis. The kidney 1 week after anastomosis showed evidence of obstruction with developing hydronephrosis. There was an increase in size with a marked congestion of surface vessels. When the bowel-ureter was opened the end of the ureter had separated from the bowel where it had been sutured with 0000 chromic catgut. It presented an edematous stump almost completely obstructed. This edematous stump of ureter was cut away leaving about 2 mm. of thickened ureter protruding within the bowel lumen. Due to edema of the wall, the lumen of the ureter was narrowed to about one-third of its normal diameter, but the urine poured out in a stream. It was thought that when the edema subsided that this would make a satisfactory anastomosis.

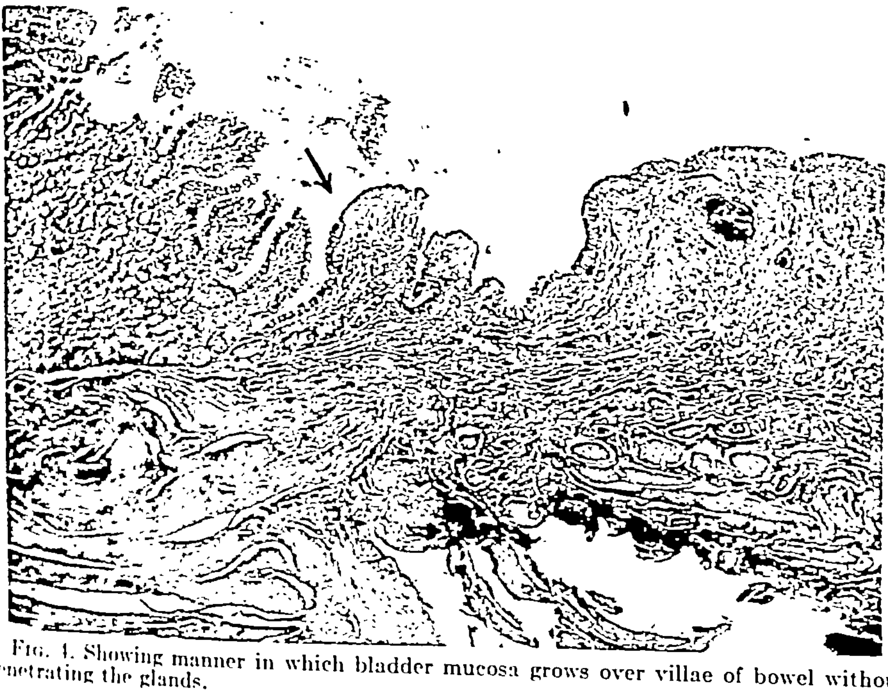

FIG. 4. Showing manner in which bladder mucosa grows over villae of bowel without penetrating the glands.

Two weeks after this second operation the normal right kidney was removed. Within 105 hours the dog became ill and died; 3 hours before death the non-protein nitrogen was 429. mg. per cent but the CO_2 was still 35.8 volumes per cent. Autopsy showed an extreme grade of hydronephrosis with complete blockage of the ureter by scar tissue, in fact the ureter could scarcely be identified as such.

Following this experience we returned to the use of cotton, exposing as little of the suture material as possible to the urinary stream.

In the last of these 3 dogs (Dog No. 8) we removed the right kidney 120 days after the left ureter had been replaced by a loop of bowel. Figure 5 shows the three stages in which this dog was operated. After each operation the nonprotein nitrogen rose and then returned to the preoperative level. Eleven weeks after right nephrectomy the nonprotein nitrogen was 35 mg. per cent and the CO_2 was 45 volumes per cent.

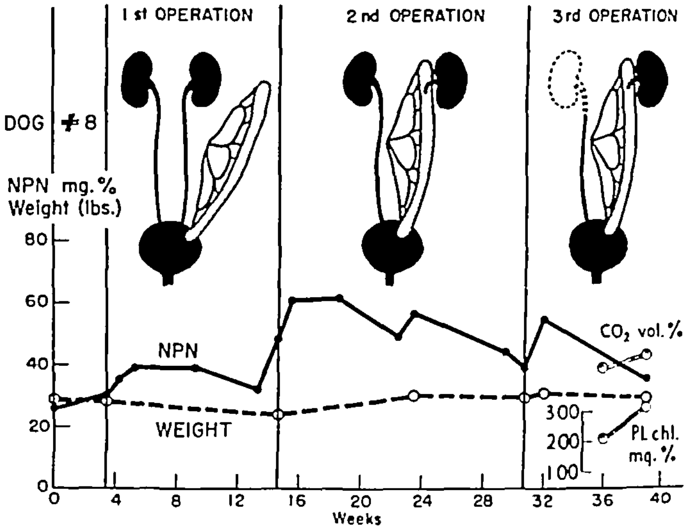

FIG. 5. Showing stages in which dog No. 8 was operated, effect of nonprotein nitrogen, CO_2, plasma chlorides and body weight.

TABLE 1. *Effects of absorption*

DOG NO.	PL. CHL. MEQ/L. (AVER.)	CO_2 VOL. % (AVER.)
Group 1. Absorption of urine possible		
1	79.3	38
3	83.0	36
6	79.3	47
8	73.2	37
11	86.3	39
Average	80	39.4
Group 2. Absorption of urine not possible		
10	83.5	38
15	82.3	50
Average	82.8	44.0

ABSORPTION OF URINARY PRODUCTS

In order to study the effects of the absorption of urinary products from the isolated loop, we studied the plasma chloride and CO_2 in 7 dogs. In five of these animals the urine was in contact with the bowel and the other two were normal dogs used as controls. In the group where absorption of urinary products was possible, the average plasma chloride level was 2.8 mEq. l lower and the plasma

CO_2 4.6 volumes per cent lower than in the normal dogs. Table 1 shows in detail the results of this study. Each figure represents an average of 4 determinations in each animal.

TABLE 2. *Bacteriology of the urinary tract*

DOG NO.	TYPE OF OPERATION	AT OPERATION	CULTURES 3 MOS. P.O. (Cath)	6 MOS. P.O. (Cath)	9 MOS. P.O.
1	Bowel Bladder L. ureter	—	E. coli A. aerogenes P. aeruginosa	P. aeruginosa A. aerogenes Gram neg. rods Not identified	—
3	Bowel Bladder B. ureters	—	P. aeruginosa Strep. viridans	P. aeruginosa Strep. viridans Prot. vulgaris	(Aspir. blad) Strep. viridans E. coli (Ureth. swab) Strep. viridans E. coli
6	Bowel Bladder B. ureters	—	P. aeruginosa Prot. vulgaris	P. aeruginosa Prot. vulgaris Strep. viridans	(Aspir. blad) E. coli
8	Bowel Bladder L. ureter at 3 mos. R. nephr. at 6 mos.	(Aspir blad) Neg. 36 hrs. (Irrig. bowel) Neg. 36 hrs.	E. coli Strep. viridans	E. coli Strep. viridans Staph. albus	(Aspir. blad) E. coli Strep. viridans Staph. albus (Ureth. swab) E. coli Strep. viridans Staph. albus
9	Bowel L. ureter	(Aspir. blad) Neg. 36 hrs.	A. aerogenes Gram neg. rods Not identified	—	(Aspir. blad) Neg. 48 hrs. (Cath) M. aureus hemol. Hem. strep. (Ureth. swab) M. aureus hemol. Hem. strep.
10	Bowel	(Aspir. blad) Neg. 36 hrs.	—	—	(Aspir. blad) Neg. in 36 hrs.

The failure of the plasma chloride to show any elevation over that in normal dogs seems to indicate that in this experiment the chloride level of the blood was not affected by absorption from the isolated loop.* The difference of 4.6 volumes per cent in plasma CO_2 is thought not to be significant in the dog.

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* Since microscopic examination disclosed no significant alteration in the loop of bowel used as ureter for 1 year, we are here assuming that its power of absorption has not been impaired. A study of this phase of the problem is now in progress.

BACTERIOLOGICAL STUDIES OF THE URINE

Repeated cultures of the urine were made in 6 dogs shown in table 2. Aspiration cultures were made from the urinary bladder at the time of the initial surgery in 3 cases; all were negative. A second aspiration culture at the end of 9 months was still negative in 2 dogs whose bladders had not been anastomosed to the bowel.

All catheterized specimens were positive, even in the normal dogs whose aspirated bladder urine was negative. This was true in spite of the fact that we took every precaution to avoid touching the vaginal wall in the passage of the catheter and employed scrupulously aseptic technique throughout. Cultures from the urethra in three of these dogs showed exactly the same organisms as the catheterized bladder urine. The principal organisms were E. coli, A. aerogenes, P. aeruginosa with an occasional Streptococcus viridans and Staphylococcus albus.

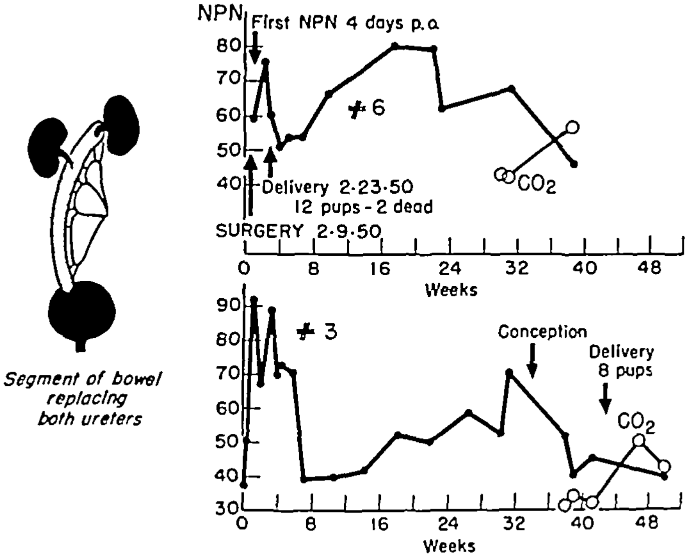

FIG. 6. Showing effect of substituting isolated segment of small bowel for both ureters. Dog No. 6 was 7 weeks pregnant at time of surgery. Dog No. 3 conceived about 8½ months following surgery.

Finally in 2 dogs a loop of bowel was used to replace both ureters at one operation. Figure 6 shows the level of the nonprotein nitrogen following surgery. Dog No. 6 was about 7 weeks pregnant at the time of surgery. Fourteen days later she gave birth to 10 living and 2 dead pups. They appeared to be full term all were destroyed. This dog appeared clinically well but ran a rather erratic nonprotein nitrogen. However at the end of 40 weeks the nonprotein nitrogen was 42 mg. per cent and the CO_2 55 volumes per cent. Now 16 months after operation the dog appears entirely normal.

Dog No. 3 showed a precipitate rise of nonprotein nitrogen from a preoperative level of 37.6 mg. per cent to 50.5 mg. per cent at 48 hours and 92. mg. per cent at the end of 96 hours. It dropped to 67. mg. per cent 10 days after surgery and fluctuated for 3 weeks, falling to the preoperative level at the end of 7 weeks. For the next 26 weeks there was a gradual increase in the nonprotein nitrogen level which was not reflected in any way in the clinical appearance of the animal. This dog, an Irish Setter, was taken out in the country for a few weeks where she exhibited entirely normal behavior, getting pregnant, delivering and nursing 8 healthy pups, all of which grew and developed normally. At the end of 50 weeks (7 weeks after the pups were born) her nonprotein nitrogen was 42, mg. per cent and the CO_2 45 volumes per cent. This dog, now 18 months after replacement of both ureters by a segment of small intestine, appears clinically normal.

CONCLUSION

In the dog a segment of small intestine can be used to replace one or both ureters without changing the clinical appearance of the animal. In most cases the nonprotein nitrogen returns close to the preoperative level. A dog with both ureters replaced by a segment of small intestine can go through a normal pregnancy and remain clinically and physiologically well at the end of 18 months.

A study of the plasma chloride and CO_2 fails to indicate any significant retention of urinary products.

All of the dogs in which the bowel was connected with the urinary bladder showed a persistent infection of the urinary tract. (No treatment was given during the course of this study.) This infection leads to a variable degree of pyelonephritis and is constant complication in this series.

Stricture and obstruction at the site of uretero-intestinal anastomosis is the most serious complication. This was the cause of death in two of the 3 dogs in which nephrectomy was performed.

If some measures can be devised to control or prevent the infection and the strictures at the site of anastomosis, we believe that this procedure will be feasible in clinical surgery.

DISCUSSION

Dr. Reed M. Nesbit (Ann Arbor, Mich.): We are indebted to Dr. McLean, who is not a urologist, for bringing to us the results of his researches in this important field of investigation. The surgeon is occasionally confronted with the problem of devising a replacement for a ureter which has been destroyed by trauma, neoplasm or scar. In the past, nephrostomy has been the only procedure available to cope with this situation. Several years ago Dr. Nelse Ockerblad designed his ingenious operation of fashioning a tube from a strip of bladder wall. The Ockerblad procedure has been successfully used in bridging defects amounting to the loss of the lower third of the ureter, but has not, I believe, been useful in situations where a more extensive loss of the ureter has occurred.

Utilization of small bowel segments is not a new idea. As the authors have pointed out, this device has been used previously, but no experimental work has been reported that bears upon the feasibility of its performance.

Drs. McLean and Fais have demonstrated that the procedure can be performed safely if certain principles are adhered to: avoidance of obstruction at the site of anastomosis, and of infection in the kidney.

It is a recognized fact that when a portion of the large or small intestine is utilized as a part of the urinary transport system, there is always absorption of urinary products by the mucosa of the bowel. This does not give rise to an upset in the chemical economy of the body as long as the renal tube mechanism remains normal. But when the nephron function is impaired by infection or back pressure, it loses its ability to maintain homeostasis and disturbances in the electrolyte balance takes place.

The use of small bowel segments, as the authors have described, should prove to be safe and relatively free from hazard if the bowel is adequately prepared before operation by the elimination of bacteria, and if modern techniques are utilized to avoid stenosis at the site of anastomosis.

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GIANT VESICAL CALCULUS, BILATERAL HYDRONEPHROSIS: A CASE REPORT

JOHN W. DORSEY

Giant vesical calculus with advanced infected bilateral hydronephrosis presents a problem in surgical management. It is felt by many urologists that the danger in suprapubic lithotomy arises not from the actual removal of the calculus, but rather from the acute exacerbation of an existing pyelonephritis. The two-stage suprapubic prostatectomy has demonstrated that proper diversion of the urine will enhance the ultimate recovery of the patient. The development of chemotherapy and antibiotics has increased the safety of many urological procedures, but in our opinion they are an adjunct to treatment and cannot supplant adequate preoperative drainage. It would seem therefore that preliminary decompression of the upper urinary tract prior to suprapubic lithotomy should be performed in certain cases.

In 1921 Randall reported the surgical removal of a vesical calculus weighing 4 pounds; the patient expired 36 hours later. This is the largest human vesical calculus of authentic record. In 1919 E. C. Smith reported the successful removal of a vesical calculus weighing 2 pounds, 6½ ounces. The largest vesical calculus removed surgically with complete recovery of the patient was that reported by F. J. Lepreau and R. H. Jenkins in 1943. It weighed 2½ pounds. In both of the above cases transurethral resection of the vesical neck was performed as a secondary procedure.

The pathogenesis of vesical calculus varies in different sections of the world. P. B. Price reporting on 121 cases observed over a five year period at the University Hospital, Tsinan, China, found evidence of infravesical obstruction in only four patients, and concluded that vitamin imbalance and deficiency were the primary etiologic factors involved. Calculus and obstructive uropathy occurred in 55 per cent of American cases, according to Caulk.

CASE REPORT

J. W. N., a 35 year old white man, consulted his family physician because of a generalized exfoliative dermatitis. Incident to his general examination a scout film of the abdomen revealed a mass of calcific density occupying the true pelvis. The patient was referred to a dermatologist who felt that the dermatitis was on an allergic basis, and strongly advised against the use of excretory urography as a diagnostic measure. He gave a history of occasional nocturia. In cold weather there was frequency of one half to one hour, and the urine voided was small in amount. He would occasionally have a bilateral costovertebral angle pressure sensation which was relieved by voiding. Five years ago he noted painless gross hematuria once, and he had been told on one occasion that he had hypertension. The history otherwise was negative.

Physical examination revealed the following significant findings: Early retinal

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 28, 1951.

changes were present. The blood pressure was 230 systolic, and 140 diastolic. A firm, insensitive, relatively fixed mass was palpated in the suprapubic region. The prostate was small in size, smooth and regular in contour, and resilient in consistency. A large hard mass was palpated above the prostate. This mass was relatively fixed and on bimanual examination was found to be continuous with the previously noted suprapubic mass. A sound was introduced through the urethra easily, but encountered an obstruction at the vesical neck which imparted a grating sensation suggestive of vesical calculus.

Blood studies revealed a nonprotein nitrogen of 43 mg. per cent, calcium 9.6 mg. per cent and phosphorus 3.6 mg. per cent. The urine contained albumin 2 plus and many pus and blood cells. Plain films (fig. 1) and a cystogram showed a bladder with intact walls that was completely filled with a giant calculus.

A cystoscope was passed to the bladder by deflecting the beak beneath the stone; leverage upon the scope then made it possible to visualize the ureteral orifices. Indigo carmine appeared in faint concentration from both ureters 15 minutes after injection. Catheters were advanced with difficulty for a limited distance on both sides, and 140 cc of residual urine was aspirated from the left ureter. Cultures from the segregated kidney and bladder urines showed a heavy growth of Proteus vulgaris. The combined retrograde pyelograms (fig. 2) indicated advanced bilateral pyelonephrosis with dilated and redundant ureters.

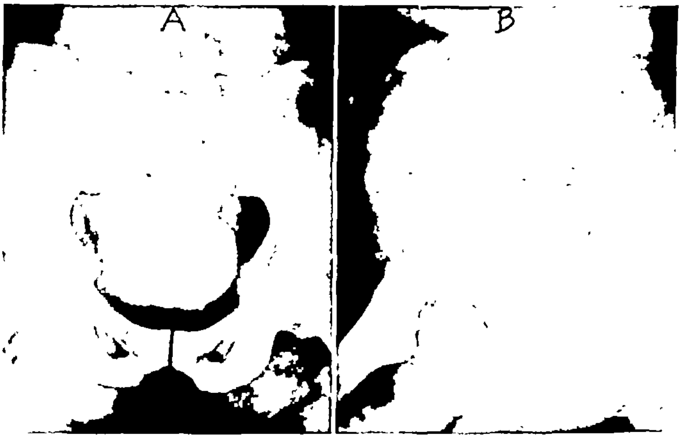

FIG. 1. A, plain urogram showing giant vesical calculus in AP view. B, right oblique position shows anterior projection of calculus.

On completion of x-ray and laboratory studies a left nephrostomy was performed by inserting a No. 18 bag catheter through the lower calyx of the kidney. Ten days later the same procedure was carried out on the right kidney, whose parenchyma had undergone marked atrophy. One week later a 2 hour differential phenolsulfonphthalein excretion showed 4 per cent from the right kidney and 25 per cent from the left.

On the twentieth hospital day a suprapubic lithotomy was performed. The vertex and lateral walls of the bladder were mobilized by a combination of blunt and sharp dissection. An elliptical incision crossing the vertex of the bladder was extended down each lateral wall in a slightly concave manner toward the base of the bladder neck. This incision created a flap of the anterior bladder wall and greatly increased the exposure. The immense calculus was firmly grasped with an abdominal tape and gently rotated as it was extracted from the pelvis. The bladder mucosa showed no evidence of neoplastic change. The fibrotic bladder neck would not admit an examining finger. A Malecot catheter was introduced through a stab wound and a tight closure of the bladder incision was effected. The removed calculus (fig. 3) weighed 455 gm.

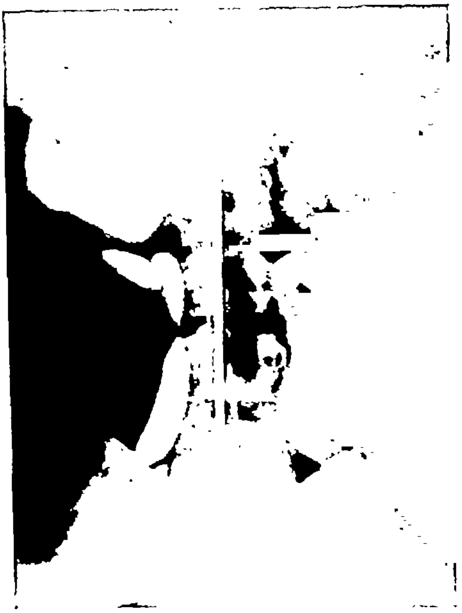

FIG. 2. Combined retrograde urogram illustrates advanced bilateral hydronephrosis, ureteral dilation and redundancy. Calcified mesenteric lymph nodes are visible over left renal outline.

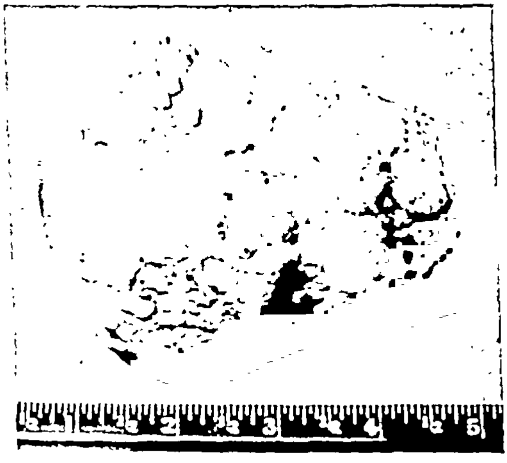

FIG. 3. Giant vesical calculus weighing 1 pound, 2 gm.

Transurethral resection of the fibromuscular tissue surrounding the bladder neck was carried out on the forty-second hospital day. Convalescence was without incident. Bilateral nephrostomy drainage was maintained for 17 days following lithotomy. At the time of release from the hospital on the forty-ninth day the patient was afebrile, ambulatory and voiding freely.

Six months following hospitalization, follow-up excretory urography showed good visualization of the left calyceal system at 30 minutes, but no visualization of the right system on the one hour exposure. However one year later retrograde urograms (fig. 4) revealed approximately a 50 per cent decrease in the degree of hydronephrosis with a corresponding change in the ureters. There has been no appreciable change in the hypertensive state, and prolonged use of the newer antibiotics has not altered the moderate infection in the residual prostate tissue. The patient is asymptomatic and has worked steadily since his release from the hospital.

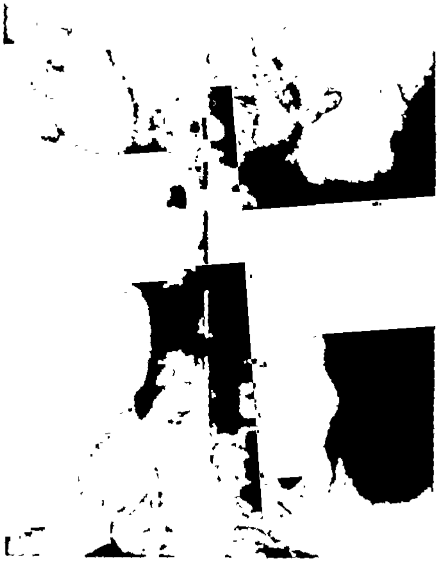

FIG. 4. Postoperative combined retrograde urogram reveals marked decrease in degree of hydronephrosis and hydro-ureter as noted in figure 2.

COMMENT

In view of the hypertension and high normal blood chemistry values this patient had undoubtedly suffered extensive renal damage. On an allergic basis a dermatologist had strongly advised against the use of excretory urography. Initial retrograde urograms were made with a realization that any instrumentation might precipitate acute pyelonephritis and that prior knowledge of the condition of each kidney would materially aid in the management of such complications. Bilateral nephrostomy made the difference between success and failure in this case. The elliptical vesical incision decreased the amount of dissection and greatly facilitated the delivery of the calculus without undue trauma to vesical mucosa and musculature. The contracted vesical neck was the probable etiological factor in the production of this calculus. The persistence of pyuria coincides with the recorded experience of other authors in the management of giant vesical calculi.

SUMMARY

A case of giant vesical calculus with advanced bilateral hydronephrosis is reported.

Bilateral nephrostomy drainage preliminary to suprapubic lithotomy was utilized.

An elliptical incision of the bladder greatly facilitated the removal of a calculus weighing 455 gm.

The etiological factor in the production of this calculus was undoubtedly the contracted vesical neck.

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SUBTOTAL CYSTECTOMY FOR ATONIC BLADDER

RAYMOND J. FITZPATRICK, LOUIS M. ORR, JOSEPH C. HAYWARD AND JAMES B. GLANTON

Insofar as can be determined, the proposal to reduce the size of the greatly dilated atonic bladder by surgical removal of the greater part of the bladder walls was first presented by one of us (L.M.O.) at the Southern Medical Association meeting in 1936. Nothing further appeared in the literature on this subject until the publication by Crabtree and Muellner in 1948, and by Fish in 1950.

Apparently Crabtree had no knowledge of the original suggestion of this procedure although he performed one such operation as early as 1937. Crabtree and Muellner reported several other similarly afflicted patients so operated upon in the years 1945 to 1947.

Fish, in 1950, reported the cases of 4 patients in whom subtotal cystectomy alone, or in combination with prostatectomy, was performed for the chronically dilated bladder. His only reference upon the subject was the report of Crabtree and Muellner in 1948.

Since the original report of subtotal cystectomy for patients with large dilated bladders, which remained despite all efforts at elimination of vesical neck obstruction, several other patients have been subjected to this procedure. The recent manifestation of interest in the subject by the foregoing mentioned authors has prompted the report of 1 case of myogenic bladder atony in a young woman and one of an atonic bladder of neurogenic origin in a man, due to tabes dorsalis.

Before presenting the results of subtotal cystectomy certain considerations relative to the different types of atony should be briefly reviewed in order to better answer the question as to whether partial cystectomy can re-establish function, partial or complete, in an atonic bladder, be it neurogenic or myogenic.

NERVE SUPPLY OF THE BLADDER

The nerve supply of the bladder is derived from both branches of the autonomic nervous system. The sympathetic innervation is from the thoracolumbar outflow. The preganglionic fibers synapse with extravesical ganglia and are then connected with the bladder by postganglionic fibers. The sympathetic nervous system constitutes the hypogastric or presacral nerve. At the present time, there is more or less unanimity of opinion regarding the fact that the sympathetic innervation has but little to do with the control of micturition. It contains some sensory fibers mediating pain and temperature and it also exercises some vascular control in the bladder walls.

The parasympathetic nerve supply (pelvic nerves or nervi erigentes) is from the sacral outflow and differs from the sympathetic innervation in that its preganglionic fibers make their synaptic connections with the visceral ganglia of the bladder. The hypogastric ganglia through which pass both branches of the autonomic nervous system are in close apposition in the male to the seminal

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Read at annual meeting, American Urological Association, Chicago, Ill., May 21, 1951 vesicles, the rectum and the inferior vesical and prostatic vessels. The nerves are heavily concentrated on the posterolateral portions of the bladder near its base where they penetrate the walls and ramify outwards in all directions to innervate the viscus. The internal pudendal nerve gives motor innervation to the external sphincter as well as to the superficial perineal muscles and the levator ani.

It is agreed by all that the parasympathetic nerves are the motor nerves of the bladder. McLellan states that the parasympathetic nerves are found to carry the essential afferent and efferent components of micturition. Stimulation of the pelvic nerves or the sacral segments of the cord causes contraction of the bladder and evacuation of urine. This occurs in the presence of the intact or sectioned presacral nerve.

BLADDER ATONY

There are two types of bladder atony, the myogenic and the neurogenic. The atonic myogenic bladder results from prolonged infravesical obstruction and is found in the late stages of bladder decompensation. Dissection and excision of the intramural ganglia of the cat's bladder result in a complete atony and as McLellan points out, it is interesting to speculate whether prolonged overdistention of the bladder, seen in cases of so-called "silent" prostatism, might not affect the intramural ganglia and produce this type of bladder. It is interesting to speculate further along these lines. If overdistention of the bladder produced by vesical neck obstruction could thus effect the intramural ganglia, do we not, therefore, in a chronically distended bladder, have both a combination of atonic myogenic and atonic neurogenic bladder, or to coin a phrase "myoneurogenic" bladder.

Langworthy and Dees have shown that the atonic neurogenic bladder with overflow incontinence results when the posterior sacral roots are destroyed. This is the type of bladder that is produced by the lesions of tabes dorsalis in the human. The atony is secondary to prolonged overdistention due to lack of sensation and desire to void. An atonic phase is also observed following acute traumatic myelitis but it is not generic to the subject matter of this paper. It is only when the afferent fibers of the reflex are are destroyed that the atonic neurogenic type of bladder results. An interruption of both the afferent and efferent fibers produces the autonomous neurogenic bladder.

DISCUSSION

If a bladder is possessed of atonic muscular elements due to prolonged infravesical obstruction, the question then arises as to how subtotal cystectomy can bring about a functioning bladder musculature. The only explanation that we can offer is that the greater burden of dilatation occurs in the more distensible portions of the bladder, namely, the dome and the anterior and lateral walls. The lower third of the bladder, because of its anatomic moorings, is unable to expand and thus stretch to the point of destruction the intrinsic intramural nerve supply. It is thus quite reasonable to expect that probably a bladder of fairly normal function might be obtained as a result of surgery eliminating the nonfunctioning portions of this type of bladder. In fact, Muellner in his work upon this subject has compared the upper two-thirds of such bladders to huge bladder diverticula.

In silent prostatism a clinical picture is described of progressive loss of desire to void and finally more or less complete retention of urine, with surprisingly few symptoms, which gives origin to the term "silent." The atony may be so extreme, as McLellan points out, that the bladder shows a smooth outline rather than one of sacculation and in a majority of cases only a minimal degree of obstruction to the vesical outlet is observed. He states that to all intents and purposes such a bladder is an atonic neurogenic one and that the relief of obstruction in many cases does not allow the development of normal micturition. If the obstruction to the vesical neck is so minimal why then should one account for distention of the bladder being secondary to the vesical neck? Fundamental logic would make one reason that either there is or there is not bladder neck obstruction. If there is, then there should develop to begin with the hypertrophic bladder musculature with gross trabeculations and cellules and only subsequently the atonic stage. Theoretically on cystography one should anticipate an irregular rather than a smooth bladder outline. What precisely is meant by the term "minimal" obstruction? One questions whether the bladder can progressively go on to further and further dilatation with evidence of only "minimal" vesical neck obstruction. May not a neurological lesion, difficult to diagnose by ordinary neurological subjective and objective studies, be present to account for this situation? In cases of so-called "silent" prostatism we believe that if such a progressive overdistention of the bladder does take place to the extent that sensation is ultimately destroyed, should there not have been symptoms in existence at the time the bladder sensibilities were still intact? If this bladder of silent prostatism is not based on a neurological lesion then a careful history should elicit complaints of painful overdistention and great difficulty and desire for urination, at least in the early phases of this condition.

The usual treatment for the atonic neurogenic bladder, such as results from *tabes dorsalis*, is transurethral resection of the vesical neck, so oft repeated, in many cases. In the majority of instances, however, the vesical neck which, according to commonly accepted theory, is composed of the interlacing fibers of the detrusor, is also dilated. Emmett and Beare point out in their series of tabetic bladders that the amount of tissue removed was less than 5 gm. in many cases. They state that even minimal amounts of obstruction can produce vesical decompensation in the already weakened tabetic bladder. In fact, in some reports the amount of tissue removed from the vesical neck is so minimal one is led to wonder whether the apparent postoperative improvement in vesical function that is observed, is actually due to the removal of such minimal tissue. Is the explanation of good results obtained, not on the basis of minimal amount of tissue resected, but rather on the basis of further damage of nerve supply, which may be producing some antagonistic effect at the vesical neck? In those cases where minimal amounts of tissue are resected at the vesical neck and good return of vesical function follows, are we justified in concluding that the few pieces of tissue removed were per se the cause of the dysfunction? Transurethral resections where the vesical neck itself is patulous also give improvement and to say that the few pieces of tissue removed from the dilated vesical neck were obstructing the outflow, seems to be begging the question. The possibility strongly suggests itself that what actually results from transurethral resection of the outlet is not that the removal of vesical neck tissue is the major contributing factor to the successful result but that not unlikely some neural synapses within the muscles of the vesical outlet are divided in the course of the operation and that the constricting neurogenic mechanism is destroyed, resulting in a return of normal muscle balance.

Neurogenic bladders become evident soon after cord damage and before any fibrosis of the vesical outlet has taken place and there appears to be no reasonable explanation as to why young to middle age adults should have any vesical neck obstruction other than that produced from the constricting influence of an imbalance of nerve supply. Finding this constriction by resection and thus releasing the imbalance seems more reasonable as the cause for the good results attendant upon the surgery than does the simple removal of so-called "obstructing" tissue.

To bring all of these theoretical considerations down to practical applications one must make an attempt, therefore, to distinguish the type of atony that is present from the standpoint of critical evaluation of hoped-for results in the two types of disease. Clinically, in both types of bladders, there is difficulty in emptying the bladder and straining to void. However, the bladder with myogenic atony usually presents painful overdistention and desire for urination, which is absent in the bladder from a posterior sacral root lesion. However, it has been pointed out that in extreme atony from prolonged overdistention due to vesical neck obstruction there may be little evidence of sensation in the bladder or desire for urination. The sensory analysis of the bladder is extremely important in that its absence in the great majority of cases is, in itself, sufficient to diagnose a neurogenic bladder. However, one should not be led astray in discarding a diagnosis of neurogenic bladder on the basis of sensation of contraction or distention, which may persist in a small degree because it is possible that such sensation may be mediated through other intra-abdominal pathways which may be reflexly stimulated. The diagnosis of the type of atony can usually be established from a detailed history and a summation of the results of clinical evaluation, including cystoscopy, cystography and cystometry.

In the atonic neurogenic bladder, where the nerve supply is damaged beyond hope of recovery and subsequently the musculature, since an intact functioning muscle depends upon an intact functioning nerve supply, the bladder becomes a dilated functionless sac. In removing the greater part of this type of bladder it can never be hoped to obtain a functioning bladder but merely to reduce the size of a functionless sac. This smaller sac may, however, serve the patient well over many years with greater comfort than would be achieved by repeated catheter or permanent cystotomy drainage. On the other hand, in the atonic myogenic bladder, we may assume that the lower third of the bladder, because of its anatomic fixation, is spared the effects of extreme distention thus preserving that small portion of the musculature as well as a segment of its nerve supply. It is thus quite reasonable to anticipate a fairly normal functioning bladder upon proper revision of the bladder neck and excision of the inert nonfunctioning portions.

With these facts in mind we would like to present briefly two cases of subtotal cystectomy for large dilated bladders:

CASE REPORTS

Case 1. G. E. K., hospital No. 68134, a 49 year old white bookkeeper, was admitted to the Orange Memorial Hospital on August 8, 1949 with the chief complaint of nausea and vomiting of 3 months duration. Anorexia had been present for 3 months and weight loss had amounted to 10 to 15 pounds. Tabes dorsalis had been present for 15 to 20 years with loss of use of both lower extremities and almost complete loss of tone of the abdominal musculature.

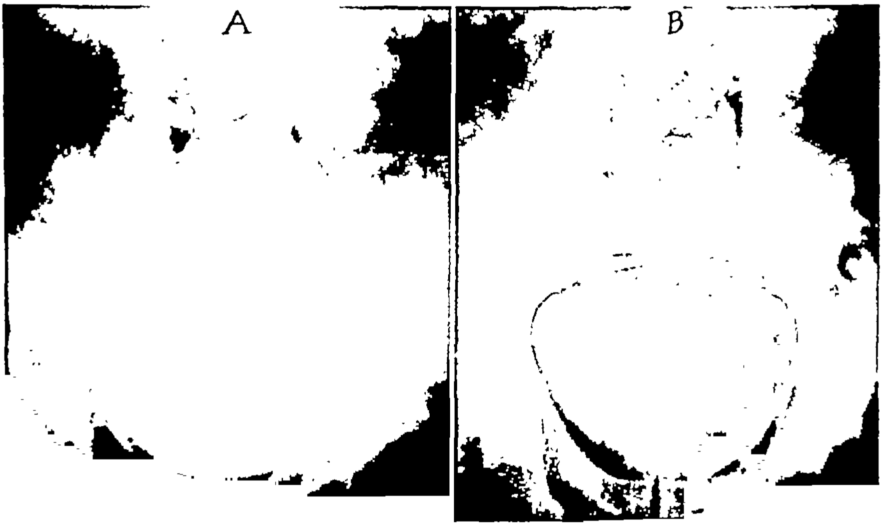

FIG. 1. *A*, preoperative sodium bromide cystogram reveals greatly distended bladder of smooth outline. *B*, postoperative cystogram shows bladder of normal dimensions.

The patient was admitted to the surgical service and after investigation surgical exploration was carried out for a large lower abdominal mass, which proved to be a huge dilated bladder with markedly thickened walls.

Subsequent urological consultation disclosed that the patient was mildly uremic at the time with a blood urea nitrogen of 43.8 per cent and voided frequently in small quantities. Complete laboratory studies were carried out and the only positive findings were mild normochromic normocytic anemia, decreased total phenolsulfonphthalein function test of 21 per cent in 2 hours, low specific gravities of the urine in the neighborhood of 1.005 and 1.007 and moderate pyuria. Residual urines varied from 1300 to 1600 cc. Although no cystoscopic evidence of vesical neck obstruction was evident, a transurethral resection was performed on August 31, 1949 and 8½ gm. of tissue were removed. Pathologically the tissue revealed fibrous tissue and chronic inflammatory changes. A postoperative cystoscopy revealed a patulous vesical outlet from which no additional tissue could safely be resected.

In spite of catheter drainage, furmethide and urecholine therapy, it was impossible to reduce the residual below 1400 to 1600 cc. A subtotal cystectomy was advised and performed on October 28, 1949. A preoperative cystogram revealed a large, smooth, dilated bladder (fig. 1, *A*). The preoperative cystometrogram revealed an atonic neurogenic bladder with a capacity of 2000 cc (fig. 2). Pathological sections of the excised tissue revealed in different areas either muscle replacement by fibrosis, marked edema of remaining bladder muscle or intrafascicular fibrosis. The bladder wall measured 2 to 2½ cm. in thickness. Chronic inflammatory changes were noted in the mucosal layer (fig. 3).

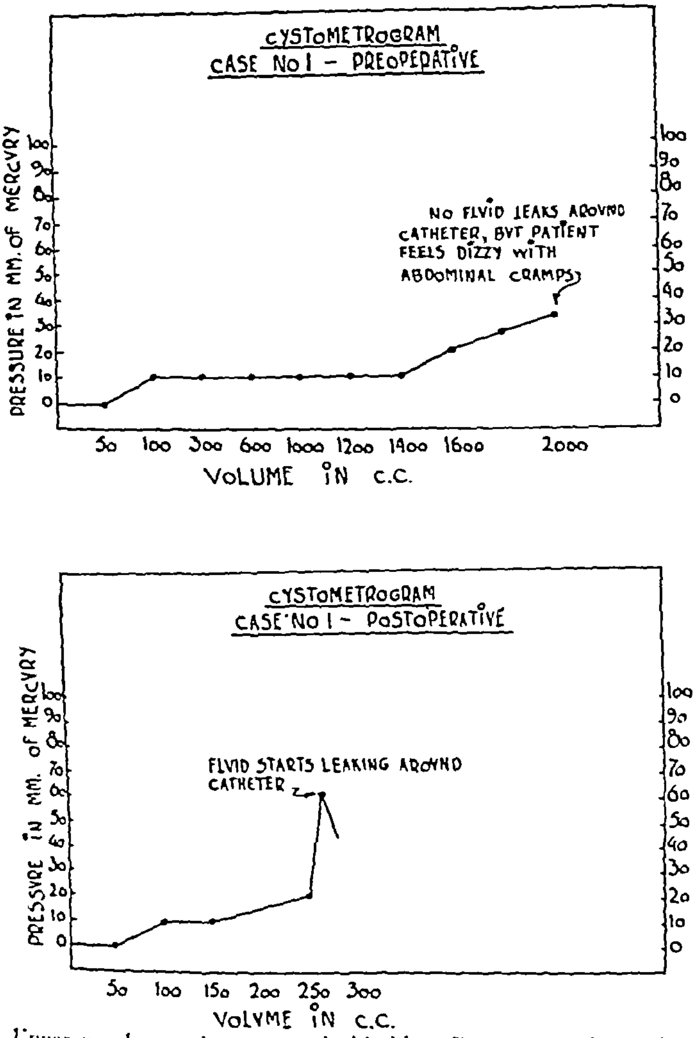

FIG. 2. Upper graph, atonic neurogenic bladder. Cystometry discontinued at 2000 cc because of symptoms. Lower graph, autonomous neurogenic bladder. Uninhibited contraction at 250 cc. Residual urine 150 cc.

Since surgery the residual urine has varied between 5 and 8 ounces and, except for urgency, voidings have been fairly normal. The postoperative cystometrogram (fig. 2) was most interesting from the standpoint that the surgical procedure apparently converted an atonic neurogenic bladder into an autonomous neurogenic bladder. A postoperative cystogram (fig. 1, *B*) reveals a reduction in size and capacity of the new bladder.

Case 2. P. S. P., hospital No. 41892, a white woman, aged 33, was first seen in September 1944, because of frequency and urgency of several years duration. The patient carried residuals during a long period of observation which varied upwards to 800 cc. Cystoscopic examination showed a marked contracture of the vesical outlet probably due to some inflammatory condition resulting in fibrosis.

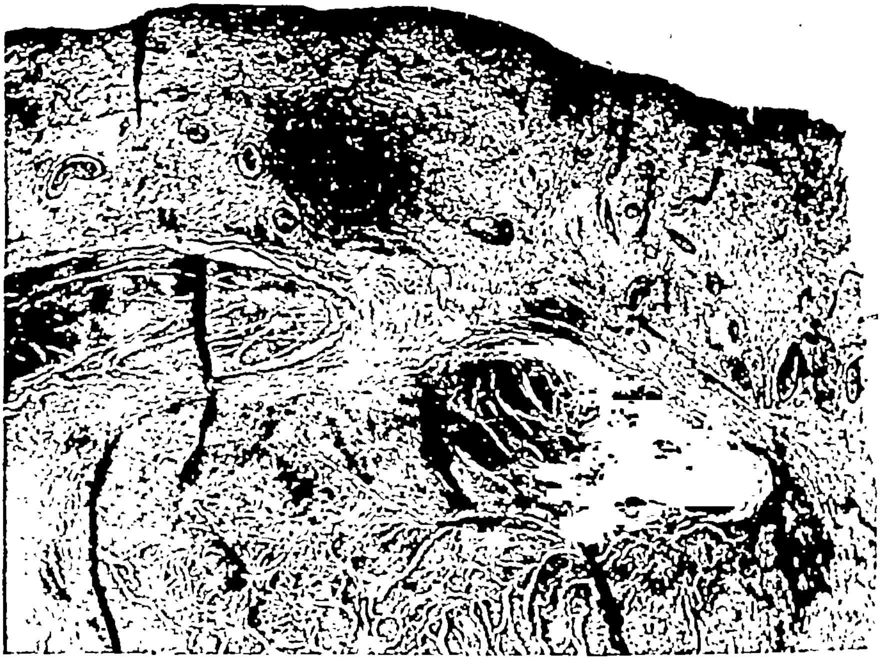

FIG. 3. Low power photomicrograph shows chronic inflammatory mucosal changes, muscle bundle edema in some areas and intrafasicular or complete fibrosis of muscle in other areas.

Transurethral resections were done in 1944, and again in 1949, for vesical outlet contractures with temporary improvement following each procedure, as evidenced by reduction of the residual urine to as low as 400 cc. However, despite urethral dilatations up to size 36F, bladder irrigations and parasympathomimetic drugs over a period of about 1 year, the residual urine again increased to more than 800 cc. Complete laboratory studies were carried out and these were all essentially within normal range save for a moderate diminution in the phenolsulfonphthalein test and moderate pyuria. Consequently in September 1950, at which time the bladder residual was still 800 cc and urinary frequency very extreme, a subtotal cystectomy was advised and performed.

The preoperative cystogram revealed a number of small cellules about the dome of a greatly dilated bladder.

On pathological examination the bladder wall measured 1.8 to 2 cm. in thickness. On microscopic section chronic inflammatory changes in the mucosa and essentially the same changes in the muscular layers, as described in the previous case, were revealed.

Since surgery her residual has never been greater than 120 cc and has more often been between 60 and 90 cc.

A postoperative cystometrogram showed a hypertonic myogenic bladder. A postoperative cystogram revealed reduction in size and capacity of the bladder.

SUMMARY AND CONCLUSIONS

It is well to keep in mind, when planning a partial removal of the bladder for myogenic atony, that the hypogastric ganglia in the male are in close apposition to the seminal vesicles, rectum and inferior vesical and prostatic vessels. It is apparent, therefore, that operations about the lower abdomen and perineum, particularly in an abdomino-perineal resection, could result in injury to the hypogastric plexus and result in a neurogenic bladder. Similarly, in subtotal cystectomies the same careful consideration must be given to the neuro-anatomical relationships, especially so in cases of myogenic atony since damage to the nerves could convert a myogenic atony into a much more serious neurogenic bladder.

Two additional cases of subtotal cystectomy in atonic bladders of different etiology are presented. Some theoretical discussions have been offered to enable one to critically evaluate the results in future surgical interventions in such cases.

1300 Kuhl Ave., Orlando, Fla.

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DISCUSSION

Dr. George O. Baumrucker (Cicero, Ill.): Dr. Orr's conclusions that this operation can be helpful at times are right. I have not performed the operation because I have not been fortunate in finding one of these large, floppy, atonic bladders. The few moderately atonic "prostatic bladders" that I have seen have all seemed to respond to suprapubic trocar drainage following which the bladder tone seemed to come back satisfactorily after 2 to 6 months.

In looking over the operative cases on all three of our urological services at Hines, I found that subtotal cystectomy was only done once for an atonic decompensated high residual bladder. I have Dr. Clay Miller's permission to present a brief summary of his operation. This one case certainly bears out Dr. Orr's conclusions:

J. D., aged 60, was first admitted to Hines January 27, 1950 with 250 cc infected residual urine. He had a transurethral resection 2 months previous to admission. Cystoscopic examination showed an apparently adequate channel but several bladder calculi and a bladder capacity of 800 cc. On February 7, 1950 the stones were removed suprapubically following which he had a recurrent suprapubic fistula for the next 5 months. He was re-admitted June 15, 1950 with a residual purulent urine of 200 cc. On June 26 and August 29, 1950, respectively, 2 gm. were resected from the bladder neck at each time. Urecholine, 10 mg. t.i.d. apparently did not help to decrease the residual urine which persisted at 200 cc. On October 14, 1950 segmental resection of the bladder wall was done, which included an area containing a small neck diverticulum of the posterior bladder wall. The piece removed was 5 by 15 cm. in size. Surprisingly enough this was followed by 200 cc residual urine which, however, decreased to a final residual of 35 cc in the course of the next month.

The following slide is from a review of 105 cases of abdominoperineal resections of the rectum for carcinoma. The first graph shows a persistent and severely hypotonic bladder still present 2 months following resection of the rectum, the active pressure being only 30 cm. of water. The second slide shows a return of bladder tone 16 months following the abdominoperineal resection, immediate postoperative tone being 40 to 60 cm. of water, while 16 months later, the active pressure was 80 to 90 cm. of water with no medication.

Of the 105 cases reviewed, only four showed a troublesome persistent residual urine. Two were believed due to a more severe damage to the parasympathetics associated with a greater degree of hypotonicity than is usually seen, and 2 more were believed due to an associated pericystitis with an associated painful reflex retention. One of the patients who had persistent residual urine due to cystitis and perineal pain was finally relieved by cordotomy. Several of the other persistent hypotonic bladders were relieved with small doses of urecholine, as is shown in the third slide. Here the postoperative active pressure was increased to 80 cm. of water and the residual urine decreased from 200 cc to 20 cc under small doses of urecholine.

Urecholine has not been found satisfactory on old flaccid bladders of long duration. Therefore I would say that in these atonic high residual decompensated bladders, if a transurethral resection or suprapubic drainage for from 2 to 6 months does not bring back a satisfactory tone and shrinkage, then the subtotal cystectomy that Dr. Orr has recommended to us should certainly be considered.

Col. J. C. Kimbrough (Washington, D. C.): Dr. Orr has rendered a great service to urology by developing this procedure. However, he is guilty of dereliction by withholding his report for so many years. I did not use this measure until 1948.

The failure to restore normal micturition following the adequate removal of bladder neck obstruction is often the result of changes in the bladder muscle due to prolonged overdistention. The muscle tissue in these cases shows atrophy, scarring and replacement by fibrous tissue. Such muscle has lost the power of contraction and expulsion of urine. It had been noted that residual urine often was not relieved by adequate bladder neck resection.

Bladder muscle has remarkable recuperative powers. Muscle injury is usually replaced by scar tissue. However, it has been proved by clinical experimentation and animal experimentation that injury or resection of the bladder and ureteral muscle is repaired by regeneration of muscle tissue.

At the time of Crabtree's report in the *Journal of Urology* (October 1948) there was, at Walter Reed Hospital, a patient of this type who had not responded to the usual operative procedures on the bladder neck. Resection of the atonic bladder wall gave satisfactory results.

A six year old boy was first admitted to Walter Reed Army Hospital December 4, 1947 with suprapubic cystostomy, resulting from abdominal exploration, at which time the large bladder was found. The final diagnoses were: bladder neck obstruction, congenital; bladder diverticulum; hydronephrosis, bilateral. He had the following operations performed: resection of the bladder neck; nephrostomy, left; diverticulectomy. Following these procedures, adequate urinary stream was established but 300 cc residual urine was present. Resection of the redundant bladder, November 8, 1948, resulted in cure.

An 8 year old boy was admitted to the hospital February 5, 1951, with a previous history of frequent urination over a period of several years. The mother noticed that after urination, it was necessary for the child to repeat the act in 5 minutes. Attacks of chills and fever were noted for 4 months previous to admission. The following diagnoses were established: bladder neck obstruction, congenital; atonic bladder with 350 cc of residual urine; bladder diverticulum. Operations performed were: diverticulectomy; partial cystectomy, resection of bladder neck. The result was a cure.

Dr. Joseph C. Hayward (Orlando, Fla.): The belief has been expressed by some that adequate transurethral resection of the vesical outlet will most often suffice in establishing normal bladder function and reduction of large residual urines in patients with neurogenic or cord bladder. This fact is admitted as being quite true in the majority of instances of neurogenic bladders when the tonus of the abdominal muscles is not impaired but where this abdominal tone is lost the results have not been altogether satisfactory.

It has been generally accepted that the removal of sometimes only a few grams of tissue from the vesical outlet is sufficient to restore a neurogenic bladder from a state of total urinary retention to a bladder of fairly normal function.

A studious investigation of the complexities of the nerve supply to the human bladder suggests very strongly the possibility that what actually results from transurethral resection of the outlet is not that removal of vesical neck tissue is the major contributing factor to the successful result, but that not unlikely some neural synapses within the muscles of the vesical outlet are divided in the course of the operation and that the constricting neurogenic mechanism is destroyed, resulting in a return of normal muscle balance.

Neurogenic bladders become evident soon after cord damage and before any fibrosis of the vesical outlet has taken place and there appears no reasonable explanation as to why young to middle age adults should have any vesical neck obstruction other than that produced from the constricting influences of an imbalance of the nerve supply. Dividing this constriction by resection and thus releasing the imbalance seems more reasonable as the cause for the good results attendant upon the surgery than does the simple removal of so-called obstructing tissue.

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UROLOGIC ABNORMALITIES ASSOCIATED WITH CONGENITAL ABSENCE OR DEFICIENCY OF ABDOMINAL MUSCULATURE

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AND (by invitation)

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The prime purpose of this report is to describe the abnormalities of the urinary tract which we found associated with the syndrome of congenital absence or deficiency of abdominal musculature and the methods of treatment which we employed. Fifty-seven cases have been described in recent splendid reviews of this condition (Eagle and Barrett, Housden, and Silverman and Huang). We wish to report 5 cases, 1 of which (case 1) was reported in part previously (Daut and associates).

The syndrome occurs predominantly in males; of the total 61 cases reported, including our own, the patient was female in only 3 instances. The basic feature of the syndrome is partial or complete absence or deficiency of the transverse, rectus, internal and external oblique abdominal muscles. The most common abnormality of the urinary tract is hypertrophy and dilatation of the bladder which may assume tremendous proportions. Extreme dilatation and tortuosity of the ureters with obstruction at the ureteropelvic or ureterovesical juncture have been reported. Hydronephrosis, cystic degeneration and atrophy of the kidney have been observed. Patent urachus, obstructions at the vesical neck and atresia of the urethra have been noted. Other common anomalies are bilateral cryptorchidism, "pigeon breast" deformity, malrotation of the gastrointestinal tract and some form of talipes.

Two theories of the cause of this syndrome are commonly proposed. The first theory, and the one to which we ascribe, was postulated by Stumme in 1903. He suggested that obstruction at or distal to the vesical neck exists in utero and results in distention of the bladder with secondary ureteral dilatation and hydronephrosis. As a result of pressure by the distended bladder against the abdominal wall, atrophy of the muscles occurs. The second theory suggests that faulty development of the abdominal musculature is the primary defect, and that the urinary abnormalities are secondary. Proponents of this theory believe that absence of the abdominal muscles, which constitute accessory muscles of urination, permits incomplete emptying of the bladder with resultant dilatation of the bladder, ureters and kidneys.

Thus, according to each of the commonly accepted theories, the destructive changes in the upper part of the urinary tract are secondary to vesical distention, and it is our opinion that surgical efforts directed toward relief of this distention should be made. Therefore, proceeding on a principle previously tried

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and proved that vesical distention has its basis in an imbalance of the detrusor urinae muscle and the vesical neck (Emmett), we performed resection of the vesical neck in 4 of our 5 cases with gratifying results; complete atresia of the urethra precluded this operation in the fifth case.

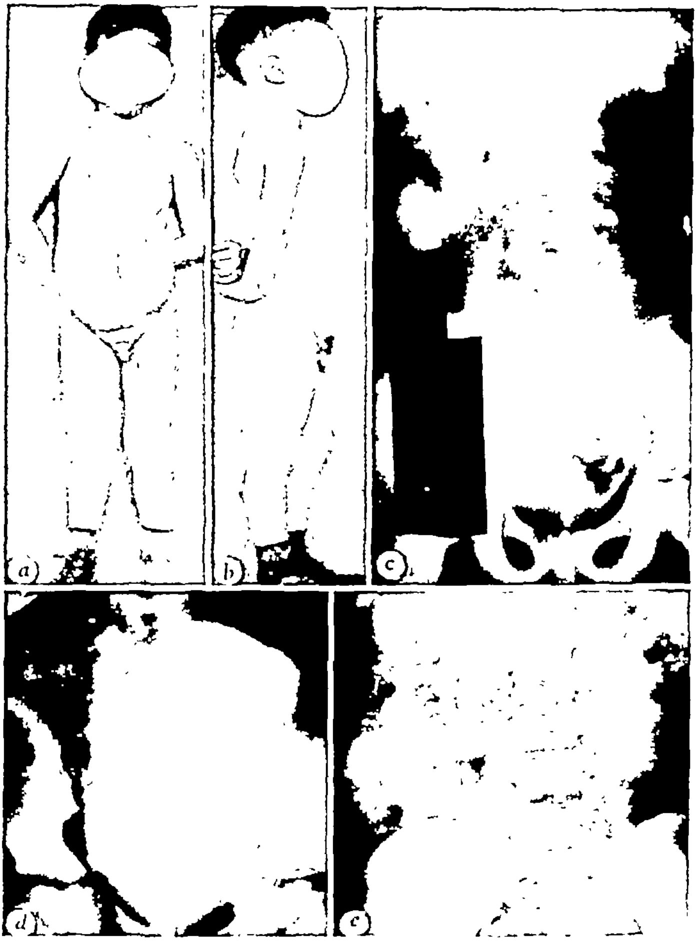

FIG. 1 (case 1). *a* and *b*, Anteroposterior and lateral views of asymmetric deformity of abdomen with midline crease. *c*, Excretory urogram in May 1945. Moderate right hydronephrosis and nonfunctioning left kidney are noted. Tremendous right ureterectasis poorly shown. *d*, Retrograde cystogram. Large, irregular vesical outline is shown. *e*, Excretory urogram made in March 1951. Right hydro-ureter is visualized better but there is no essential change as compared with *figure 1c*.

REPORT OF CASES

Case 1.—A boy, 3½ years old, was brought to the Mayo Clinic in May 1945, because "an absence of his stomach muscles" had been noted since birth. The child had experienced recurrent episodes of fever and constant dribbling of urine. Physical examination disclosed a well-nourished child with a large protuberant abdomen which deviated toward the right (fig. 1*a* and *b*). The upper portions of the rectus muscles were present, but the remaining abdominal muscles were absent. A mass considered to be an enlarged right kidney was noted in the right flank in addition to a distended bladder. Bilateral cryptorchidism was present and slight dribbling of urine was noted.

Urinalysis revealed pyuria, grade 4, and an occasional red blood cell; micrococci were grown by culture. The value for urea was 44 mg. per 100 cc blood. Determination of residual urine disclosed 400 cc.

An excretory urogram revealed moderate dilatation of the pelvis and calyces of the right kidney and enormous dilatation of the right ureter (fig. 1*c*). There was no evidence of a functioning left kidney. A cystogram disclosed a huge vesical shadow which extended up to the fourth lumbar vertebra (fig. 1*d*). It was noted that the child remained dry for a period of 6 to 8 hours following removal of residual urine at which time urinary dribbling appeared.

A sound of 16F caliber was passed easily and cystoscopic examination disclosed a large atonic bladder which was not trabeculated. The base of the bladder appeared elevated and the interureteric ridge hypertrophied. Neither ureteral orifice was positively identified. The vesical neck particularly in the region of the floor appeared obstructive. Consequently a transurethral resection of the vesical neck was carried out in May 1945, utilizing a perineal urethrostomy. Three grams of tissue were removed and microscopic study of this tissue revealed hyperplasia of muscle and inflammatory reaction.

After removal of the catheter improvement in the size of the stream was noted, but urgency was present A suitable corset was fashioned for the patient. At the time of dismissal the amount of residual urine was 125 cc. Determinations of residual urine were made regularly and urinary antiseptic agents were administered intermittently at home. The amount of residual urine gradually fell to an ounce or less and urination improved considerably; urinary leakage practically ceased.

Improvement continued, and at our request the patient returned for reexamination in February 1946. At that time vesical function was almost normal. The escape of a few drops of urine was noted when he was excited or engaged in strenuous exercise; there was no leakage of urine at night. Urinalysis disclosed pyuria, grade 1, and the urea content of the blood was 32 mg. per 100 cc. No residual urine was present and a 16F sound passed easily. By excretory urography it was noted that the pyelocaliectasis of the right kidney had appreciably decreased, although the tremendous dilatation of the right ureter remained unchanged. There was no excretion of contrast medium by the left kidney.

The child returned for his yearly examination in June 1947, at which time his mother stated that urination was normal; dribbling of urine was avoided by having the child void at regular intervals. During the past 16 months the child had experienced four attacks of chills and fever associated with cloudy urine which responded promptly to treatment with penicillin. Urinalysis disclosed pyuria, grade 3, and an occasional erythrocyte. Streptococcus faecalis was obtained by culture of the urine, and the amount of residual urine was 10 cc. The improved appearance of the right kidney was maintained as shown by excretory urography. The use of urinary antiseptics was advised and the patient was dismissed.

The patient returned in November 1948, for re-examination. His mother stated that the attacks of chills and fever occurred with greater frequency and that he complained of pain in the right lower quadrant of the abdomen during these attacks. Urinary control was excellent and the urinary stream normal. A firm, nontender mass, 3 cm. in diameter, was palpable in the right lower quadrant of the abdomen.

Urinalysis revealed pyuria, grade 3, and hematuria, grade 1; the appearance of the right kidney and ureter was unchanged as shown by excretory urography. Cystoscopy disclosed the prostatic urethra and vesical neck to be open widely; attempts at catheterization of the right ureter were unsuccessful.

It could not be determined whether the patient's symptoms and the small abdominal mass were related to the dilated right ureter or possibly epididymitis in association with the undescended right testicle. In view of the patient's good general condition surgical intervention was considered inadvisable and the patient was dismissed and advised to receive intermittent chemotherapy.

The patient returned for his annual examination in July 1950. He had experienced no further bouts of infection since the time of his last examination; his general health was excellent and he had no urinary symptoms. The small abdominal mass noted previously was no longer palpable.

Urinalysis yielded negative results and the urine was sterile; 35 cc of residual urine were found. Excretory urography revealed no change in the upper part of the urinary tract. The patient was dismissed and advised to return in one year.

The patient returned in March 1951, with no complaints or urinary symptoms. In the interim since his last examination he had experienced one attack of chills and fever, pain in the right renal region and dysuria which responded to treatment with penicillin. The patient's mother believed that the caliber of the urinary stream was decreased since that attack.

Urinalysis yielded negative results and the urine was sterile; 20 cc of residual urine were noted. The upper part of the urinary tract appeared unchanged as shown by excretory urography (fig. 1c). Cystoscopy revealed slight narrowing of the external urethral meatus and meatotomy was performed. Sounds up to 18F in size were passed easily and the bladder appeared normal except for hypertrophy of the interureteric ridge. The vesical neck was open widely.

The meatotomy and urethral dilatation resulted in considerable increase in caliber of the urinary stream and the patient was dismissed and advised to return in 1 year.

Comment on case 1: -This patient has been observed for a sufficient length of time to permit evaluation of therapy. It is our belief that resection of the vesical neck halted the progressive destruction of the upper part of the urinary tract and prevented death due to uremia. For the past year the patient has been asymptomatic, his urine has remained normal, there has been no residual urine and good renal function has been maintained. Mild pyelocaliectasis of the right kidney and enormous dilatation of the ureter persist, but there has been no progression since resection of the vesical neck was performed—a period of 6 years. In view of his excellent health we prefer continued observation rather than plastic procedures on the ureter. We surmise that the left kidney is atrophic.

Case 2.—A boy, 6 years old, was brought to the clinic in April 1946, because of a large abdomen, which had been noted at birth, and recurrent urinary infections. The patient had been ill practically throughout infancy. He had experienced feeding problems, slow gain in weight, constipation and frequent mild to severe respiratory infections. Two years before admission he had recurrent attacks of fever, and a diagnosis of infection of the urinary tract had been made and chemotherapeutic drugs prescribed with but slight beneficial effects. The child's thirst appeared insatiable and his mother estimated that he drank a gallon of water daily. Vesical function was apparently normal.

Physical examination disclosed a funnel-shaped chest with flaring of the costal margins. The abdomen was large and protuberant and an absence of the lower half of the rectus and oblique abdominal musculature was noted (fig. 2*a* and *b*). The liver and spleen were readily palpable and bilateral cryptorchidism was noted.

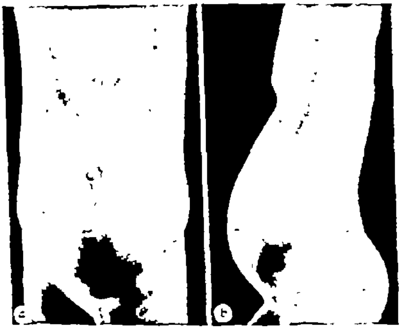

Fig. 2 (case 2). *a* and *b*. Anteroposterior and lateral views of symmetric deformity of abdomen with midline crease.

Urinalysis disclosed pyuria, grade 4, and hematuria, grade 1; streptococci and micrococci were noted by culture. The value for urea was 56 mg. per 100 cc blood. The presence of 400 cc residual urine was determined. Excretory urography disclosed moderate dilatation of the pelvis and calyces of the right kidney; there was no evidence of a functioning left kidney (fig. 3*a*). A retrograde cystogram revealed a large, smooth sacculated vesical outline (fig. 3*b*). Definite hypertrophy of the posterior commissure of the prostate which resulted in a deep gutter between the verumontanum and vesical neck was noted by cystoscopic examination. The trigone appeared normal; the left ureter was catheterized and only an extremely dilated ureter was outlined by pyelography (fig. 3*c*).

In view of the severe recurrent infections of the urinary tract it was considered best to perform left nephro-ureterectomy first, and this was carried out in April 1946. The kidney was atrophic, and almost complete destruction of the parenchyma was noted. The redundant ureter was approximately equal in size to the child's colon. The kidney and ureter weighed 37 gm. and microscopic study disclosed atrophy of the kidney. Convalescence was uneventful. An abdominal support was fitted and the patient was dismissed with instructions to return for further studies.

The child returned in June 1947. In general, his health had been good except that he appeared to tire easily and had poor appetite. He had had no urinary symptoms, but repeated urinalysis had revealed severe pyuria. Urinalysis at this visit disclosed pyuria, grade 4, and an occasional erythrocyte; culture of the urine was reported to be sterile, although many gram-positive cocci were noted. The urea content of the blood was 60 mg. per 100 cc and the residual urine measured 140 cc. The urographic appearance of the right kidney was unchanged.

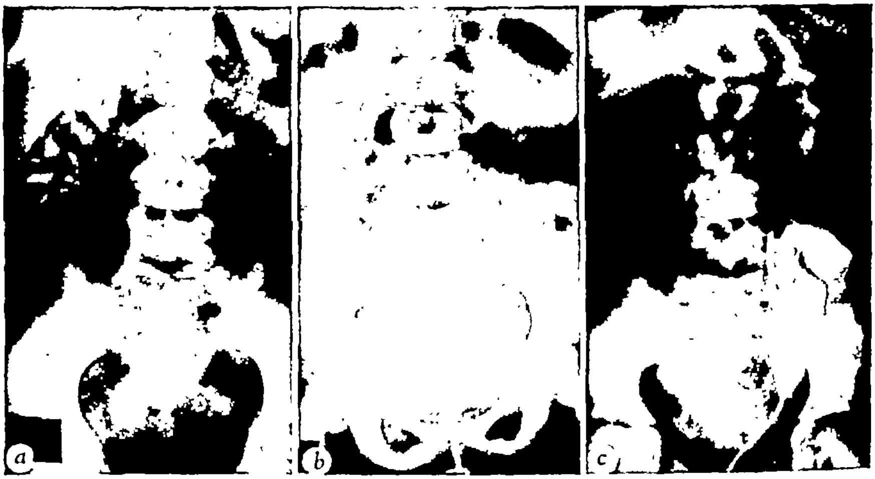

FIG. 3 (case 2). *a*, Excretory urogram. Moderate right hydronephrosis and nonfunctioning left kidney are noted. *b*, Retrograde cystogram. Enlarged vesical outline with sacculation is apparent. *c*, Left retrograde pyelogram. Extreme dilatation and tortuosity of left ureter are present.

In July 1947, resection of the vesical neck was performed with the infant resectoscope. Two grams of tissue were removed and microscopic examination of this tissue disclosed inflammatory muscle.

After resection the patient voided satisfactorily and the amount of residual urine decreased to 50 cc. The child was dismissed from our care and advised to receive intermittent chemotherapy and have monthly determinations of residual urine.

In response to inquiry in November 1947, the patient's mother stated that the child was in good health and "from his actions one wouldn't know there was anything wrong." He had no urinary symptoms and the last determination of residual urine disclosed only 15 cc. Subsequent attempts to contact the patient have been unsuccessful.

Comment on case 2: Recurrent severe infections of the urinary tract necessitated removal of the functionless left kidney. Resection of the vesical neck was followed by a gratifying decrease in the amount of residual urine, and four months later the child was apparently entirely well. Unfortunately efforts to learn of the patient's further course have been futile.

Case 3.—A boy, 4 years old, was brought to the clinic in March 1947, because the mother had noted the appearance of swellings on each side of the child's abdomen during exercise. Dribbling of urine both during the day and night was noted.

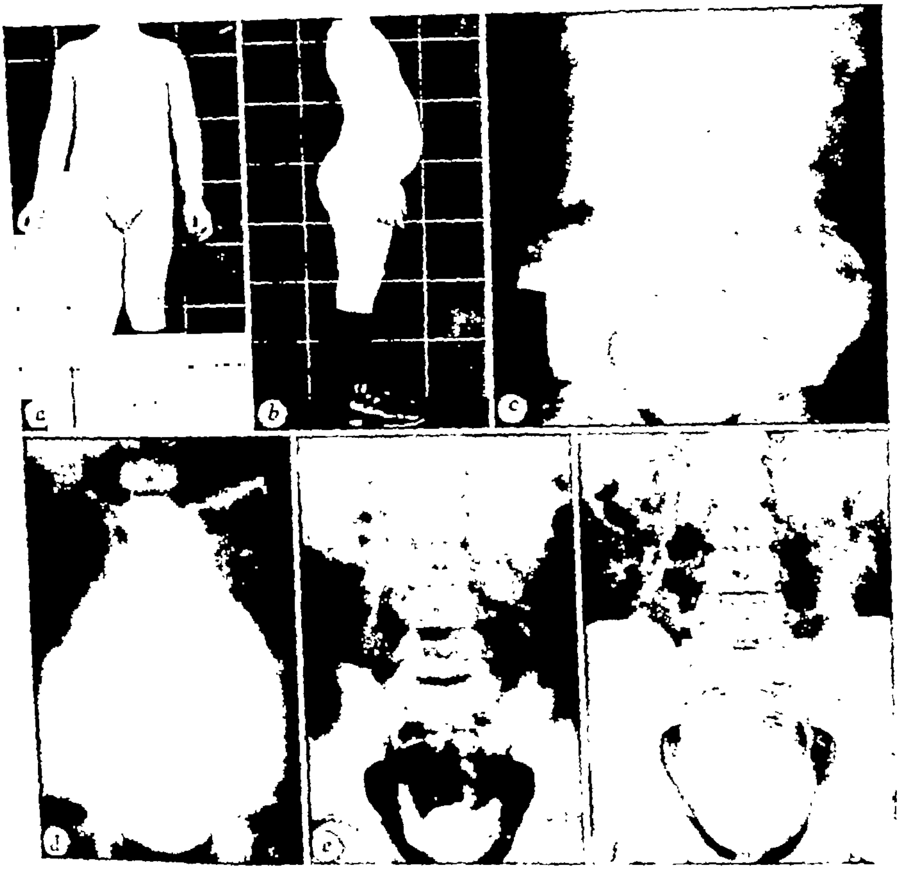

FIG. 4 (case 3). *a* and *b*, Anteroposterior and lateral views. Protuberant abdomen is somewhat masked by child's obesity. *c*, Excretory urogram made in 1947. Upper part of urinary tract is poorly visualized but lower right ureterectasis is well shown. *d*, Retrograde cystogram made in 1947. Extreme vesical dilatation is noted. *e*, Excretory urogram made in 1950. Striking decrease in size of vesical outline as compared with figure 4*d*. *f*, Excretory urogram made in 1951. Increased caliectasis of the right kidney as compared with figure 4e. Right ureterectasis is unchanged and vesical outline appears normal.

Physical examination disclosed a large obese boy, who was 20 pounds overweight. A marked bulge was noted in the left flank when the patient strained, and the skin over the abdomen appeared redundant in spite of the obesity (fig. 4*a* and 4*b*). A small ventral hernia was present above and to the right of the umbilicus and there appeared to be incomplete absence of all the lower abdominal muscles particularly on the left side. Bilateral cryptorchidism was present.

Urinalysis gave negative results and a culture of the urine was sterile. Excretory urography disclosed mild caliectasis on the right and marked irregular dilatation of the lower third of the right ureter; minimal dilatation of the calyces of the left kidney was present (fig. 4*c*). Two determinations of residual urine yielded 500 and 600 cc respectively. A retrograde cystogram showed a large, rounded, smooth vesical outline which extended up to the third lumbar vertebra (fig. 4*d*). Cystoscopy disclosed a large smooth bladder with considerable redundancy of the tissue of the trigone. The right ureteral orifice was gaping; the left appeared normal and catheterization of either ureter was impossible. No obvious obstruction at the vesical neck was noted.

It was decided to perform resection of the vesical neck because of the large amount of residual urine and the large flabby bladder. This operation was carried out through an external urethrotomy in April 1947, and 4 gm. of tissue from the vesical neck were excised. Microscopic examination of this tissue disclosed an inflammatory reaction in the muscle. Convalescence was delayed owing to drainage of urine through the perineal wound, but this soon ceased and the wound healed.

Prior to dismissal the patient was able to void a larger excellent stream and his mother stated that his abdomen no longer appeared distended. An abdominal support was fitted, chemotherapy was suggested and the child was dismissed with advice to return in three months.

The child was returned in August 1947, and the mother stated that he had been well during the interim. He was able to void an excellent stream, and involuntary dribbling of urine occurred only if he delayed urination and permitted his bladder to distend.

Urinalysis disclosed pyuria, grade 1, and no residual urine was found. An excretory urogram revealed the upper part of the urinary tract to be unchanged. The patient was dismissed and advised to return for re-examination in six months.

The patient returned in February 1948. His mother stated that his health had been good. His urinary stream was excellent in caliber and involuntary dribbling of urine occurred only at times when he wore the abdominal support and delayed urination for more than three hours. Urinalysis gave negative results and the urine was sterile. The urea content of the blood was 32 mg. per 100 cc. A 12F catheter was passed easily and no residual urine was found. The urographic appearance of the upper part of the urinary tract was unchanged. A retrograde cystogram showed considerable reduction in size of the vesical outline. The patient was dismissed and advised to return in two years.

The patient returned in April 1950. His mother stated that his urinary control had improved considerably; incontinence of urine occurred only rarely and at times of great activity. Urinalysis gave negative results and there was no residual urine. The urea content of the blood was 28 mg. per 100 cc. An excretory urogram revealed increased caliectasis of the right kidney; the right ureter and left kidney appeared unchanged (fig. 4*e*). The vesical outline was irregular but of normal size. Because of the increasing caliectasis it was advised that the child return in one year.

The patient returned in April 1951. The mother stated that during the past 6 months his urinary control had been excellent and he had experienced no urinary symptoms. Urinalysis gave negative results and there was no residual urine. The urea content of the blood was 40 mg. per 100 cc. Excretory urography disclosed increased caliectasis of the right kidney; the right ureter, left kidney and bladder appeared unchanged (fig. 4*f*). The child was dismissed and it was suggested that he return in one year, principally in order to permit study of the right kidney.

Comment on case 3:—This patient has been observed for 4 years. It is our belief that resection of the vesical neck has eradicated residual urine and urinary incontinence. The patient's health is excellent, but the increasing caliectasis of the right kidney is disconcerting. It is likely that this is due to ureteral reflux, and if the caliectasis continues to increase, re-implantation of the ureter into the bladder may be necessary.

Case 4.—A boy, 2½ years old, was first seen elsewhere in February 1948, because of constant drainage of urine through an opening in the lower part of the abdomen; the child had never voided through the penis. He had not walked because of a deformity of the right foot. He had not started to talk but made peculiar noises which sounded like attempts at talking. His abdomen was large and protuberant and he was severely troubled with constipation.

Physical examination disclosed normal vocal cords. The abdomen was protuberant and flabby and the lower parts of the rectus, oblique and transverse abdominal muscles were absent (fig. 5*a* and *b*). The peritoneal contents were easily palpable through the thin abdominal wall. The bladder was distended, and pressure over the vesical area resulted in a discharge of urine from a patent urachus 5 mm. in diameter. Bilateral cryptorchidism was present. Although the penis was well developed, the external urethral meatus was represented by a shallow recess and the corpus spongiosum could not be palpated; the prostate gland was not palpable. The right foot consisted of a heel with attached toes. Merrill-Palmer tests revealed that the child's mental age was 3 years.

Urinalysis disclosed pyuria, grade 1, and cultures of the urine were sterile. Nonprotein nitrogen in the blood measured 50 mg. per 100 cc. Visualization of the upper part of the urinary tract by excretory urography was unsatisfactory owing to gas in the bowel; it was possible to determine only that two kidneys were present.

The recess in the tip of the glans penis was probed but no opening was detected. A catheter was passed through the patent urachus and a cystogram disclosed an irregularly dilated bladder which, in lateral view, appeared attached to the anterior abdominal wall (fig. 5*c* and *d*). Cystoscopy through the patent urachus revealed slight trabeculation of the bladder and a well-formed trigone; attempted catheterization of the ureters was unsuccessful. The vesical neck was represented by a depression which ended blindly.

Bilateral uretero-sigmoidostomy was considered the procedure of choice and was carried out in March 1948. Both ureters appeared dilated and the bladder [illegible]. Three days after operation the nonprotein nitrogen content of the blood dropped to 29 mg. per 100 cc. Convalescence was uneventful and the postoperative urogram, in which structures were still obscured by gas, disclosed greater concentration of medium in the kidneys. An abdominal corset and a prosthesis for the foot were obtained and the child was dismissed. Ten days after dismissal the patient experienced an attack of acute pyelonephritis which subsided rapidly after chemotherapy, and he was again dismissed.

His condition remained good for approximately one year, but thereafter slow, gradual deterioration developed. He was readmitted to the hospital in July 1949, in a state of coma; the nonprotein nitrogen content of the blood was 195 mg. per 100 cc. Therapy was futile and the patient died two days after admission; permission for necropsy was refused.

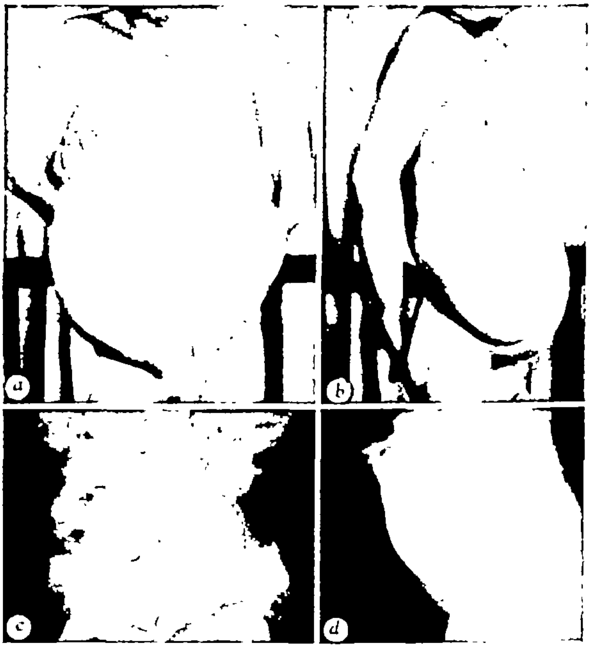

Fig. 5 (case 4). *a* and *b*, Anteroposterior and lateral views. Slight asymmetric enlargement of abdomen. *c*, Cystogram, anteroposterior view. Irregular outline of the dilated bladder is shown. *d*, Cystogram, lateral view. Bladder appears attached to anterior abdominal wall by patent urachus.

Comment on Case 4:--The profound abnormalities present in this case precluded any therapy other than diversion of the urinary stream by ureterosigmoidostomy. Atresia of the urethra is the extreme example of infravesical obstruction resulting in distention of the bladder and subsequent hydronephrosis and hydro-ureter.

The patient in this case was treated by one of us (Culp) at the Henry Ford Hospital, Detroit, and has been included in this series through the courtesy of Dr. John K. Ormond, Chief of the Division of Urology of that institution.

Case 5.--A male infant, 5 months old, was brought to the clinic in April

1951, because of recurrent attacks of fever associated with diarrhea and constipation. Urinary symptoms had not been noted. The abdominal muscles were absent at birth.

The pertinent findings noted at physical examination were absence of the lower portions of the rectus, oblique and transverse abdominal muscles and bilateral cryptorchidism (fig. 6*a* and *b*). Intestinal movements were clearly visible; the right kidney was palpable and the bladder was distended.

Urinalysis revealed mild pyuria and culture of the urine disclosed numerous organisms (Streptococcus faecalis). The urea content was 80 mg. per 100 cc blood. Roentgenographic study of the colon revealed no abnormality. By means of excretory urography it was determined that both kidneys were functioning, but further interpretation was impossible. An unsuccessful attempt was made to determine the amount of residual urine; the largest catheter that could be passed through the urethra was a 6F ureteral catheter, and the drainage was unsatisfactory. A retrograde cystogram disclosed a large pyramid-shaped vesical outline. Both ureters were outlined and appeared markedly dilated and tortuous; the right kidney was visualized incompletely but extreme hydronephrosis was noted (fig. 6c).

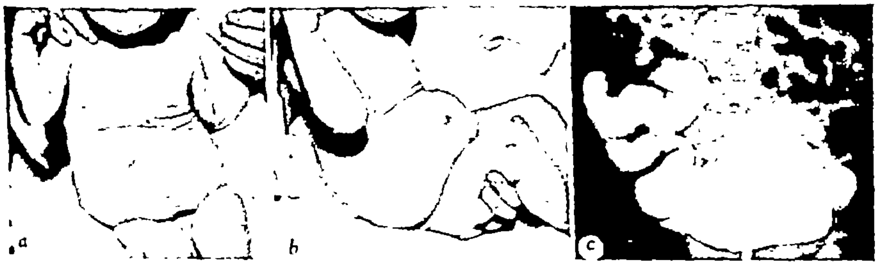

FIG. 6 (case 5). *a* and *b*, Anteroposterior and lateral views. Slightly asymmetric protuberant lower part of abdomen is evident. *c*, Retrograde cystogram. Dilatation of bladder with reflux resulting in visualization of bilateral hydro-ureters.

Cystoscopic examination disclosed a large trabeculated bladder and a constricting band of tissue extending across the posterior vesical neck from the 5 to 7 o'clock positions. The prostatic urethra and verumontanum appeared normal. The constricting band was obliterated by multiple linear incisions, and a 12F catheter was placed indwelling.

Following removal of the urethral catheter the urinary stream was excellent and the amount of residual urine was only 3 cc. The bladder was palpable as a small contracted mass. An abdominal corset was fitted and the infant was dismissed. It was advised that intermittent urinary antisepsis be employed and that the infant be returned in 3 months for re-examination.

Comment on case 5:—The immediate results of operation, namely, relief of vesical distention and eradication of residual urine, have been encouraging. However, the moderate azotemia and profound pathologic changes in the upper part of the urinary tract are ominous signs which will require further observation.

COMMENT

The abnormality of the urinary tract which was present in all cases of congenital absence or deficiency of abdominal musculature which we observed was distention of the bladder with an appreciable amount of residual urine. The changes noted in the upper part of the urinary tract were hydronephrosis and hydro-ureters of varying degree, and atrophy of the kidney. All patients were male and they had bilateral cryptorchidism.

It is our opinion that the primary pathologic problem is obstruction at the vesical neck which results in distention of the bladder and the presence of residual urine. The changes in the upper part of the urinary tract result as a consequence of the vesical distention. Thus we are in agreement with Stumme and Housden in our belief that the obstruction of the neck of the bladder occurring in utero results in distention of the bladder and atrophy of the lower abdominal muscles due to pressure by the distended bladder. The use of a snugly fitting corset or abdominal binder is an important aid in raising intra-abdominal tension to permit more effective evacuation of the urinary bladder.

It is our opinion that in patients in whom fair or good renal function is present, efforts should be directed toward relieving the primary cause of the disability, namely, the obstruction at the vesical neck. The patient's ability to void a good stream and the physician's ability to pass a urethral catheter does not preclude the presence of obstruction at the vesical neck. An absence of, or failure of the mother to note, urinary symptoms does not imply that distention of the bladder is absent. Determinations of the amount of residual urine, an important diagnostic test, are practically lacking in the cases described in the literature.

Furthermore, obstructions at the vesical neck may be difficult or impossible to appreciate even by cystoscopic examination. Actual resection of the vesical neck may be necessary to determine whether obstruction is present. If such resection results in a striking decrease in the size of the bladder and disappearance of residual urine, it may be safely assumed that obstruction of the vesical neck was present originally. Just such observations were made in the 4 cases in our series in which this procedure was possible. The relief of vesical distention and residual urine permitted eradication of infection and prevented further progressive deterioration of the upper part of the urinary tract. This part of the urinary tract is usually so profoundly altered that one cannot expect the kidneys and ureters to return to normal, even after the vesical distention has been relieved, and one must be satisfied with the existing condition.

It is obvious that some patients afflicted with this condition, when first seen, will exhibit such profound deterioration of renal function that nothing less than lifesaving nephrostomy or nephrectomy will be suitable. It is our opinion, however, that many operations such as ureteroplasty and ureterovesical reimplantation, which have been employed in this condition, deal with an effect rather than a cause.

Our appreciation is expressed to Miss Lucia Warren of Spencer, Incorporated for her invaluable aid in designing the corsets used in these cases.

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THE URINARY BLADDER IN MULTIPLE SCLEROSIS

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Previous studies of the physiology of micturition by means of fluoroscopy[1, 2, 3, 4] have led us to a concept which has differed in important respects from those currently held. In the light of this concept, the behavior of the bladder in 35 patients with multiple sclerosis has been evaluated. As a result of these observations, which form the basis of this report, we have been able to relieve these patients of some of their distressing urinary symptoms.

In this paper no attempt will be made to speculate on the extent to which each portion of the complex nerve supply of the bladder is damaged by multiple sclerosis. Such discussions are apt to be too hypothetical, and from a clinician's point of view, unrewarding. Rather shall we focus our attention on the consequences of this disease on the bladder, its associated musculature, and on the mechanism of micturition as a whole.

It will be necessary to summarize our view of the physiology of micturition in order to convey clearly what we believe to be some of the underlying factors in the altered behavior of the bladder in multiple sclerosis.

THE VOLUNTARY MECHANISM IN NORMAL MICTURITION

We have demonstrated that man has a distinct "voluntary mechanism" by means of which he starts and stops his urinary stream at will. For micturition to begin, the detrusor must contract and thus cause the reciprocal opening of the internal sphincter. In the past it had been assumed that man could directly contract his detrusor for micturition. Our studies, however, have shown that this is not so. Man utilizes a group of striated (somatically innervated) muscles with which he initiates the reflexes of micturition. Voluntary micturition begins with a slight increase in intra-abdominal pressure, which is brought about by the fixation of the diaphragm at the end of a brief inspiration, and the contraction of the abdominal musculature. The contraction of these muscles is associated with the relaxation of the muscles of the pelvic floor. The muscle in the pelvic floor which is particularly concerned with this process is the pubococcygeus, which constitutes the anterior portion of the levator ani. As a result of the increase in intra-abdominal pressure and the relaxation of the pubococcygeus, the bladder neck is pushed downwards (fig. 1). This downward "push" on the bladder

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Read in part at meeting of American Neurological Association, Atlantic City, N. J. June 14, 1950.

Aided by grant from the Massachusetts Chapter of the National Multiple Sclerosis Society.

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neck is the stimulus which causes the detrusor to contract and thus precipitates the reflexes of micturition, i.e., the reciprocal opening of the internal sphincter and of the proximal urethra. The contraction wave, which begins at the bladder neck, spreads bilaterally and symmetrically to the base, to the sides and lastly to the dome of the bladder. The voluntary inhibition of the urinary stream is carried out, not by the mere contraction of the external sphincter, as was taught in the past, but by the contraction of the entire levator ani. This elevates the bladder base, and the internal sphincter snaps shut. The urinary stream is thus promptly shut off first at the internal sphincter.

This concept of the physiology of micturition emphasizes the importance of a normally functioning levator ani and its component, the pubococcygeus. These muscles are the primary means by which man exercises voluntary control over his urinary stream, and we have therefore designated them as the "voluntary mechanism." When the function of these muscles is abolished, it becomes impossible for man to start or to stop micturition at will. Without the use of the "voluntary mechanism," micturition becomes entirely dependent on the response of the detrusor to other stimuli.

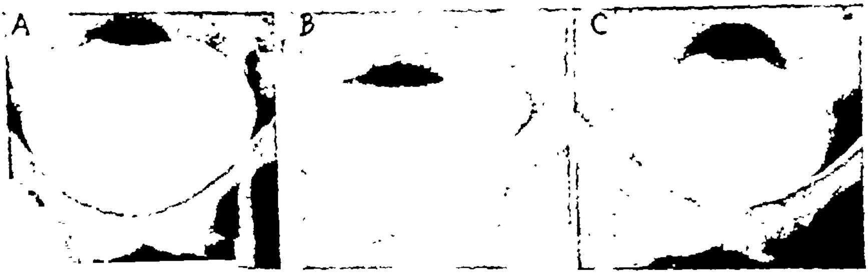

FIG. 1. Normal micturition. *A*, bladder at rest. *B*, beginning of voluntary micturition. Note that bladder neck has been pushed down for voluntary initiation of urinary stream. *C*, bladder during micturition. Sides and dome of bladder have contracted.

DISTURBANCES OF MICTURITION IN MULTIPLE SCLEROSIS

Patients with multiple sclerosis may have a normally functioning urinary tract. If the disease does produce urinary symptoms, however, they manifest themselves in the following pattern. The most common symptom is frequency of urination. If the patient is asked to record for a day or two the amount of urine voided at each urination and the time at which he voids, such a micturition record will reveal a urinary frequency of about 8 to 20 times a day, nocturia, and a voiding volume of about 15 to 90 cc per micturition. The desire to void is often quite urgent. Urgency may be accompanied by involuntary micturition, or there may be an imperceptible loss of urine while walking. Some patients have occasional attacks of acute urinary retention, during which they have some discomfort from the overdistended bladder. In the very advanced stages of the disease, painless overflow incontinence is not uncommon.

When one examines these patients, one finds that a correlation exists between the condition of the pelvic floor and the urinary symptoms, and therefore particular attention should be paid to the status of these muscles. If the levator ani, as palpated by rectal examination, is normal in tonicity and in contractility, i.e., the patient can readily tighten or relax the levators at will, there will be no serious disturbance of micturition. Micturition, however, will become quite abnormal if the levators are flaccid and the patient has lost the ability to contract or relax these muscles promptly. When such flaccidity exists the patient will not be able to start micturition at will, and will have considerable difficulty in inhibiting an urge to void, or in stopping the involuntary passage of urine.

Various degrees of deficiency in the voluntary control and in the tone of the levator ani muscles will be encountered. In some patients a considerable lag is found between an effort to contract the levators, and its actual accomplishment. Again, in others, a levator which is quite flaccid when first palpated, can be stimulated to a sharp and very spastic contraction. In advanced cases, complete and unalterable flaccidity of the levators is usually associated with an overdistended bladder, and overflow incontinence.

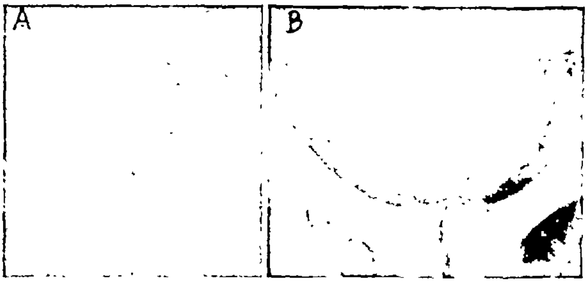

FIG. 2. *A*, hyperirritability of detrusor in multiple sclerosis. Note strong bladder spasm from mere contact of bladder with catheter. *B*, same bladder. Cystogram obtained during excretory urography. Note normal capacity.

Another condition which contributes to the urinary symptoms of multiple sclerosis is hyperirritability of the smooth muscle organs, including the detrusor, the urethra and the anal canal. It is not uncommon to find that the anal canal, which was patulous on digital examination, will, because of the stimulation from the mere introduction of the examining finger, contract to such an extent as to grip the finger tightly. Similarly, when an attempt is made to pass a catheter, the urethra too can be felt to grasp the catheter, so that occasionally it may be impossible to pass the catheter in the male. Again, when the catheter touches the bladder, the detrusor will go into spasm so that only 20 to 30 cc of fluid can be instilled into the bladder, and that only after considerable pressure. It is for this reason that cystometry in these patients may be misleading, and the erroneous conclusion made that the bladder has a very small capacity and is markedly hypertonic (fig. 2). A more physiologic method of evaluating the capacity of the bladder can be had by the cystogram which is obtained by means of intravenous urography, and by the evaluation of the micturition record, which reveals that the patient in whom one could not instill 20 cc can easily void 200 or 300 cc. While the bladder may not be as hypertonic as the cystometric curve would lead one to believe, the detrusor is nevertheless more irritable than is normally the case. It is readily stimulated to contraction by moderate increases in intra-abdominal pressure. This response of the detrusor to a sudden increase in intra-abdominal pressure tends to produce an "effort incontinence" which is characteristic of some patients with multiple sclerosis. They may lose urine when they rise from the sitting posture. Urgency and incontinence again may overtake them while they are climbing the stairs. When a detrusor contraction has been precipitated by these efforts, the patient will not be able to inhibit the bladder if he has a flaccid pelvic floor, or one that is slow to contract in response to his effort to do so. Urinary distress in patients with multiple sclerosis can therefore be ascribed to a lack of co-ordination of the muscles which constitute the "voluntary mechanism," and to interference with the co-ordinated function of the detrusor as a unit.

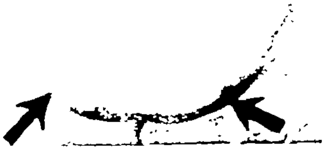

FIG. 3. Cystogram obtained during excretory urography. Arrows point to deep folds. Bladder at rest.

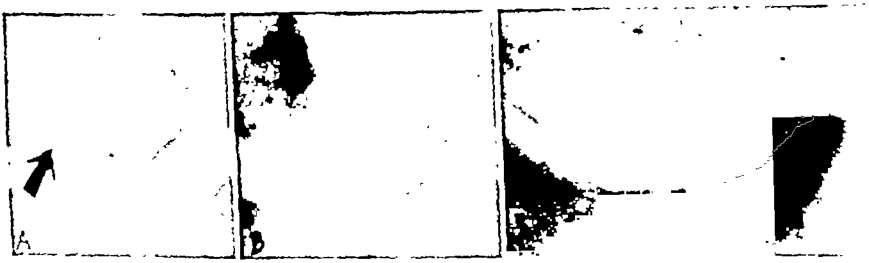

FIG. 4. *A*, female. Arrow points to pseudodiverticula. *B*, female. Note irregularly contracting detrusor with upward projection of bladder dome and pseudodiverticula. *C*, female. Note pinched off portion of bladder on right.

THE RADIOGRAPHIC PICTURE OF THE BLADDER IN MULTIPLE SCLEROSIS

In most cases of multiple sclerosis, the cystogram obtained during excretory urography shows a bladder which is about normal in capacity. The bladder wall is very apt to be thrown into deep folds (fig. 3). When the bladder is observed on the fluoroscopic screen after retrograde filling with an opaque medium, it will either contract sharply, despite the use of little pressure in instilling the fluid, or the contracting detrusor will assume a shape different from that of the normal bladder, or the usual hypertonic bladder. Instead of contracting as a unit, portions of the bladder contract independently of the rest of the organ, and the dye is thus seen to be pinched off in pockets of various size, forming pseudodiverticula (figs. 4 and 5). Women who lose urine imperceptibly while walking are apt to have a funneled bladder neck in the cystogram obtained in the erect posture. In the end stages of the disease the bladder is large and atonic, and indistinguishable from an atonic bladder due to other causes (fig. 6).

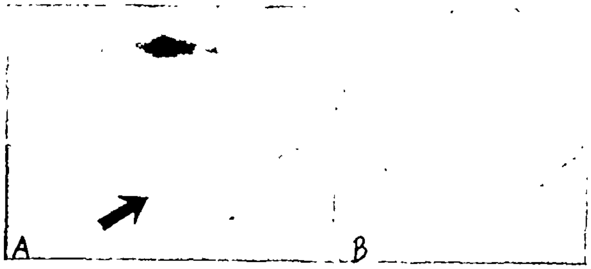

FIG. 5. *A*, female. Arrow points to funneled vesical neck. *B*, female. Bladder at rest. Note funneled bladder neck.

FIG. 6. Male. Chronically overdistended atonic bladder associated with overflow incontinence.

TREATMENT

Since the effects of multiple sclerosis on the urinary bladder are not uniform, treatment to be effective must be based on the study of the individual case. Most ambulatory patients, however, who suffer from disabling frequency of micturition, urgency, incontinence and especially from "effort incontinence" are very apt to have a bladder of about normal capacity, but one which is hyperirritable and which contracts precipitously in an incoordinated manner to cause the above symptoms. It is in this group of patients that we have been able to obtain most gratifying relief by very simple therapy. Bearing in mind the underlying pathologic physiology, it seemed reasonable to try to relax the detrusor by means of atropine. This time-tested drug proved to be remarkably successful. Detrusor irritability can be significantly lowered by atropine, thus reducing urgency and urinary frequency; the voided volume per micturition will then increase from 60-90 cc to a volume of 200-300 cc. Sudden contractions of the detrusor can be reduced to a minimum or abolished altogether by atropine and the patient will thus be spared from unanticipated loss of urine.

To achieve this relief, we have given atropine sulfate in tablets of 0.4 mg. (1/150 gr.) two or more times a day. When to administer the drug, and the amount to give, must be determined for each patient. Most patients do not mind moderate urinary frequency while they are at home. They do, however, want relief from their distressing symptoms when they leave home on shopping tours or for social visits. A tablet of atropine (0.4 mg.) taken one or two hours before such contemplated trips will calm the bladder for a period of 2 to 4 hours. Patients quickly learn to use the drug in a way to give them the comfort they need. A small dose of atropine (0.4 mg.) which has very little effect on the normal detrusor will influence significantly the bladder of multiple sclerosis. It is for this reason that patients must be taught to use this drug with caution, for it is possible to relax the detrusor with atropine to the point of complete urinary retention.

Some patients do not tolerate atropine too well and are disturbed by the blurred vision or the uncomfortable dryness of the mouth which can follow its use. In such cases the desired result may be achieved by corresponding doses of panparnit or by amphetamine sulfate in doses of 20 mg.[5] once or twice a day.

Patients who have a large, atonic and overdistended bladder with overflow incontinence may benefit by temporary catheter drainage. The detrusor is put at rest and permitted to regain some of the tonicity which it has lost by the overstretching of its musculature. Urecholine chloride in doses of 5 to 20 mg. by mouth two or three times a day may in some cases aid in the recovery of detrusor tonicity. In selected cases of persistent atony of the bladder, micturition can be improved by transurethral resection of the internal sphincter.[6]

A few examples will illustrate what can be done to relive the severe urinary symptoms of multiple sclerosis.

Case 1. BHH No. 86857A, L. F., aged 30, had multiple sclerosis for 5 years. Since the onset of his disease he had had to wear a penis clamp because of involuntary loss of urine by day and by night. The urine was mildly infected. The rectal sphincter and the levators were flaccid, and responded slowly to his efforts at contraction. He voided 30–90 cc urine 9 times during the day and 4 times during the night. The urine was cleared with antibiotics. He was then given atropine sulfate in doses of 0.4 mg. 4 times a day. This enabled him to discard the penis clamp during the day, for the past 6 months, although he still wears it at night to insure a dry bed. He now voids 150–200 cc 4 or 5 times a day and once during the night.

Case 2. A. D., aged 45, a private patient, had multiple sclerosis 6–8 years, and marked urinary symptoms for the past three years. She had to void about 20 times during the day and an equal number of times at night. The voided volume of urine ranged between 15–100 cc. This patient also had marked incontinence, for which she wore plastic underclothing, and large pads. The bladder urine was purulent and contained E. coli. The rectal sphincter was patulous, but the patient could contract the rectal sphincter and the levator ani muscles after some effort. The urinary tract infection was cleared with aureomycin. This reduced the urinary frequency somewhat. She was then given atropine sulfate, 0.4 mg.

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[5] Loman, J., Grossberg, B. and Myerson, A. Human autonomic pharmacology XIX. The effect of mecholyl, prostigmine, benzedrine sulphate and atropine on the urinary tract: cystometric studies. N. Eng. J. Med., 219: [illegible], 1938.

[6] Emmett, J. L. Transurethral resection and treatment of true and pseudo cord bladder. J. Urol., 53: [illegible], 1945.

3 times a day and before retiring. On this regimen her frequency decreased to 8 times a day, and the nocturia practically disappeared. The bladder capacity increased to about 250 cc. Her incontinence subsided and she is now able to discard the plastic underclothing and the large pads.

Case 3. BIH No. 56972, H. T. aged 33, had multiple sclerosis 7 years. For the past 2 years the patient voided 10–12 times during the day, 3–4 times during the night, and suffered from urgency, incontinence. The rectal sphincter was patulous, but the patient was able to contract her levators. The urine was uninfected. Atropine sulfate 0.4 mg. twice a day reduced the urinary frequency to 5 times during the day and once at night. Urgency incontinence was satisfactorily controlled.

Case 4. BIH No. M10229, R. G., aged 35, had multiple sclerosis for 8 years. For the past 2 years the patient had been bedridden or confined to a wheelchair because of inability to walk. Since then he had imperfect control of his rectal sphincter, and dribbled urine incontinently. The bladder was distended to the umbilicus, and contained about one liter of urine. The rectal sphincter was patulous, and he could neither contract his sphincter nor his completely flaccid levators. Temporary catheter drainage was instituted to put the bladder at rest, and urecholine chloride in doses of 5–10 mg. a day was administered, in an effort to restore detrusor tonicity. This was not successful. The bladder neck was then resected transurethrally. Following this operation the patient could empty his bladder down to a negligible residual with the aid of manual compression, and was thus relieved of his constant urinary dribbling.

SUMMARY

In the light of recent concepts of the physiology of micturition, 35 cases of multiple sclerosis have been investigated. The urinary symptoms of urgency, frequency, and incontinence were found to be due to the effect of this disease on the function of the muscles of the pelvic floor, and to a peculiar hyperirritability of the detrusor. The contractility of the detrusor as a unit tends to disintegrate in multiple sclerosis, and portions of the bladder are prone to contract independently, to form pseudodiverticula.

The functional integrity of the detrusor can be re-established to a good extent by the judicious use of atropine, amphetamine sulfate, or similarly acting drugs, and the distressing urinary symptoms favorably influenced.

Drugs, such as urecholine, combined with temporary catheter drainage of the bladder are of value in restoring detrusor function after occasional attacks of urinary retention.

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RESIDUAL URINE, AN IMPORTANT FACTOR IN INTERPRETATION OF CYSTOMETROGRAMS. AN EXPERIMENTAL STUDY

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It has been known for some time that interruption of the parasympathetic innervation of the bladder produces an organ which after 2 to 3 weeks shows a large increase in the thickness of the vesical wall.[1-5] Unilateral bladder hypertrophy is said to occur after section of the sacral roots on one side,[2, 3] but this finding has not been confirmed.[6] According to Langworthy and Kolb,[2] histological changes in the mucosa suggest that infection and irritation may be the cause of the hypertrophy. However, Carpenter[6] found bladder hypertrophy after section of the preganglionic parasympathetic nerve supply even when infection was prevented by appropriate chemotherapy.

Interruption of the parasympathetic innervation of the bladder is followed, of course, by urinary retention. In general, animals which have the largest residual urines show the greatest increase in bladder weights.[6] To test the hypothesis that bladder wall hypertrophy and low volume-pressure curves are related to the presence of residual urine rather than to preganglionic parasympathetic denervation alone, we have diverted the urine from the bladder. This prevents changes in intravesical volume in animals in which the preganglionic parasympathetic fibers to the bladder can be cut. At various times after the operations the pressure-volume relations of the organ have been studied. Finally, the animal was sacrificed, the bladder weighed, and in some instances histological examinations of the bladder wall were made.

All operations were performed aseptically under intravenous pentothal anesthesia. The thin posterior peritoneum of the dog makes it difficult to prepare ureterocutaneous anastomoses without entering the peritoneal cavity. A single midline lower abdominal incision for exposure of the ureters with separate lateral stab wounds through which the renal stumps of the ureters were brought was unsatisfactory, since strictures of the ureters occurred at the site of the stab wounds. Successful ureterocutaneous anastomoses were obtained by making an oblique incision through the abdominal wall on each side. After isolating and sectioning each ureter, the renal ends were swung in a wide curve anterolaterally and brought through the upper ends of the oblique incisions where they were sutured in place. The several layers of the body wall were closed in the usual way. Immediately after the operation the bladder was catheterized and any urine present was evacuated. Irritation of the skin of the anterior abdomen by the continuous flow of urine was minimized by shaving the skin carefully, by daily washing, and by sponging with alcohol. If infection occurred, aureomycin was administered.[6]

Cystometric measurements. Preoperative control measurements were carried out under light pentobarbital anesthesia. The sacral roots were infiltrated with 2 per cent procaine in order to abolish the detrusor reflex. Under this circumstance volume-pressure determinations can be made over a wider range of volumes than is possible when reflex activity is present.[8] With aseptic technique, 10 cc increments of sterile water were admitted through a No. 16 Foley catheter retained at the vesical neck. The bladder contents were connected through a continuous column of water with a water manometer which was adjusted to zero pressure at the level of the symphysis pubis. Readings were taken only after the pressure elevations resulting from filling had decreased to consistent resting values. We have used the term bladder capacity as the volume of fluid in the viscus at an intravesical pressure of 15 cm. of water.

RESULTS

Volume-pressure relations. When the bladder of a normal dog lightly anesthetized with pentobarbital was filled with successive 10 cc increments of fluid the resting intravesical pressures slowly increased to 8 cm. of water at a bladder volume of about 140 cc. At this point contraction of the detrusor muscle occurred, suddenly increasing the intravesical pressure to some 70 cm. of water. Infiltration of the sacral roots with 2 per cent procaine did not change the shape of the volume-pressure curve, but since in these animals the detrusor reflex was absent, volume-pressure measurements could be made over a wide range of volumes (fig. 1, A). In some experiments as much as 400 cc of fluid were admitted into the bladder, the intravesical pressure rising to 20 cm. of water. The bladder capacities were read from the volume-pressure curves and tables 1 and 2 show that dogs weighing between 9.2 and 26 kg. have bladder capacities which vary between 170 and 360 cc.

The volume-pressure curves of bladders of 5 dogs in which the ureters were transplanted some days previously were measured. At the time of the determinations the animals were lightly anesthetized with pentobarbital and the sacral roots were infiltrated with procaine. Seven to 39 days after transplantation of the ureters the maximum amount of fluid which could be admitted to the bladder did not exceed 50 cc. As shown in fig. 1, *B* the volume-pressure curve was remarkably steep even 5 days after the ureters were exteriorized. The bladder capacities amounted to only 5 to 17 per cent of the control values (table 1).

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[8] Carpenter, F. G. and W. S. Root. Am. J. Physiol., **166**: 686, 1951

In 6 dogs the ureters were transplanted and the posterior roots were sectioned. Four to 28 days after root section, the volume-pressure curves showed the same

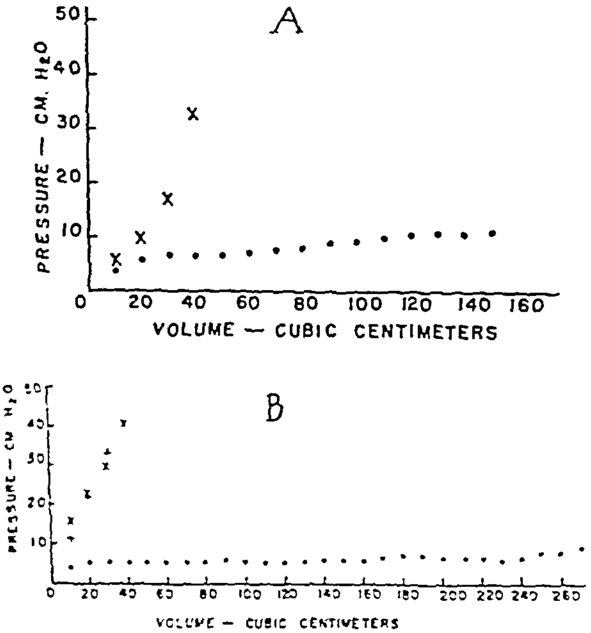

FIG. 1. *A*, Volume-pressure relations shown by bladder of dog 5, lightly anesthetized with pentobarbital: (●) before operation. 2 per cent procaine infiltration of sacral roots at level of S2 and 3; (X) 39 days after ureteral transplantation and immediately after *section of sacral roots*. *B*, volume-pressure relations shown by bladder of dog 1, lightly anesthetized with pentobarbital: (●) before operation, 2 per cent procaine infiltration of sacral roots at level of S2 and 3; (X) 7 days after ureteral transplantation and immediately after section of sacral roots; (+) 11 days after ureteral transplantation and 4 days after *section of sacral roots*.

between 490 and 1000 mg. per kg. of body weight (table 3). The application of statistical methods showed that these bladder weights fall within the range of twice the standard deviation of the normal series.

Histological examinations of the bladder walls were made. Paraffin sections were stained with hematoxylin and eosin. The mucosal, muscularis and serosal layers of specimens taken from animals 3 or more weeks after sacral root section and transplantation of the ureters were indistinguishable from those of normal animals.

TABLE 1. *Bladder capacities of dogs before and at various times after transplantation of ureters (sacral roots infiltrated with 2 per cent procaine)*

DOG NO.*	WT. IN KGMS.	CONTROL CAPACITY, CC	TIME AFTER OPERATION, DAYS	CAPACITY AFTER URETERAL TRANSPLANTATION, CC
1	10.5	270	7	15
2	12.9	250	15	25
3	14.9	200	19	10
4	26.0	290	28	50
5	12.5	200	39	25

* Each dog has been assigned a number which is not changed in the different tables. Thus, dog No. 1 in each of the three tables is the same animal, etc.

TABLE 2. *Bladder capacity of dogs before and at various times after transplantation of ureters and bilateral section of sacral roots*

DOG NO.	WT. IN KG.	CONTROL CAPACITY, CC.	CAPACITY AFTER URETEROSTOMY AND SACRAL ROOT SECTION, CC	CAPACITY MEASURED	
				Days after ureterostomy	Days after root section
1	10.5	270	9	11	4
6	10.5	330	55	7	7
7	15.0	360	17	18	18
8	9.2	170	26	18	18
9	10.5	230	48	20	20
8	9.2	170	22	28	28

TABLE 3. *Bladder weights of dogs at various times after transplantation of ureters and section of sacral roots*

DOG NO.	WT. IN KG.	WT. OF BLADDER, GM.	TIME AFTER SACRAL ROOT SECTION, DAYS	BLADDER WT. MG. PER KG. BODY WEIGHT
5	12.5	8.3	4	660
4	26.0	16.2	6	620
1	10.5	6.7	11	640
9	10.5	6.4	20	610
7	15.0	15.0	27	1000
8	9.2	6.8	28	740
6	10.5	5 2	33	490

DISCUSSION

The relation of volume to intravesical pressure has been used for many years as an index of the physiological state of the urinary bladder and its reflex pathways. It is well known that interruption of the parasympathetic innervation produces an organ which retains large volumes of residual fluid with only moderate increases in pressure. The foregoing results indicate that the physiological state of the constantly empty bladder is very different from that of the organ which is periodically filled and emptied as in the normal animal or from the condition of the bladder in which retention is present. Within a few days the empty bladder shows a very steep volume-pressure curve, the capacity being only a fraction of the control values. The changes in the volume-pressure curves of empty innervated bladders are the same as those shown by the empty organ in which the preganglionic parasympathetic fibers have been cut. These findings suggest that the intravesical pressure developed at any given volume depends upon the previous history of the organ in terms of the degree of filling and presumably the amount of fiber stretching to which the bladder muscle has been subjected.

The microscopic structure of the bladder wall of dogs in which the ureters have been transplanted is indistinguishable from that of the normal animal. This is true even when the sacral roots have been sectioned and the animal kept for 3 or more weeks. In such dogs the weights of the bladders do not increase above those of the normally innervated, periodically emptying organs of normal dogs. The results indicate that in the absence of residual urine, bladder hypertrophy does not occur after preganglionic parasympathetic denervation. These findings emphasize the importance of preventing the accumulation of urine before complete clinical evaluation of bladder function can be made. We do not know whether it is better to remove residual urine by direct gravity or by tidal drainage.

SUMMARY

The bladder capacities (volume at an intravesical pressure of 15 cm. of water) of 10 normal dogs varied between 170 and 360 cc (tables 1 and 2).

In 5 dogs the maximal amount of fluid with which the bladders could be filled, 7 to 39 days after ureteral transplantation, did not exceed 50 cc. The bladder capacities amounted to only 5 to 17 per cent of the control values (table 1, and fig. 1).

When the ureters were transplanted and the pressure-volume relations of the bladder measured 4 to 28 days after bilateral section of the sacral roots (6 dogs), the same changes were found as after ureteral transplantation alone (table 2, fig. 1, *B*).

The microscopic structure of the bladder wall of dogs in which the ureters have been transplanted and the sacral roots sectioned 3 or more weeks previously is indistinguishable from that of normal animals.

The absolute bladder weights or the bladder weights in mg. per kg. of body weight of dogs in which the ureters have been transplanted and the sacral roots sectioned bilaterally fall in the same range as those of normal animals (table 3).

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VARIATIONS IN MORPHOLOGY OF URINARY BLADDER EPITHELIUM. SPECIAL REFERENCE TO CYSTITIS GLANDULARIS AND CARCINOMAS

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The importance of interpreting the variations in the epithelial pattern of the urinary bladder in inflammatory and neoplastic conditions is evidenced by the numerous articles which have appeared in the literature.[1] Two forms of cystitis glandularis are recognizable: the most common type involves the trigone and the new formed glands in this condition bear a striking resemblance to those of the prostate; secondly, glands which are similar to those of the large intestine may, with less frequency, be found in the dome of the bladder. Similarly, adenocarcinomas may be of two types: those resembling the adenocarcinomas of the prostate and those resembling the adenocarcinomas of the colon. It must therefore be assumed that the vesical mucosa has a dual origin, entodermic in the dome and mesodermic in the trigone. The interpretation of adenocarcinomas of the bladder is frequently of paramount importance. Because of their resemblance to carcinomas of the prostate and to carcinomas of the colon, they may be mistaken for metastatic lesions Furthermore, because the trigone is derived from the wolffian duct and is therefore related to the prostate, one must consider the possibility of hormonal imbalance in the development of cystic trigonitis and must reflect on the possibility of palliative hormonal therapy in carcinomas of the trigone, especially the adenocarcinomas. For a better understanding of the variations in morphology of the epithelium of the urinary bladder, it is necessary to review the embryology of this particular part and the associated structures because metaplasia, cataplasia and neoplasia frequently reflect histogenesis.

HISTOGENESIS[2]

At the end of approximately two weeks development the human embryo reaches the three layer stage, an upper layer of ectoderm, an inferior layer of entoderm and a middle layer of mesoderm (fig. 1). It should be noted that from the time of inception the cells which constitute the ectoderm and entoderm

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[1] Morse, H. D.: Etiology and pathology of pyelitis cystica, ureteritis cystica and cystitis cystica Am J. Path., **4**: 33, 1928.

Joelson, J. J. Pyelitis, ureteritis and cystitis cystica. Arch. Surg., **18**: 1570, 1929.

Patch, F S and Rhea, L V The genesis and development of Brunn's nests and their relation to cystitis, cystitis glandularis and primary adenocarcinoma of the bladder Canad M A.J., **33**: 507, 1935.

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Hoyt, H S: Cystitis cystica as a single tumor J Urol, **59**: 421, 1948

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Torassa, G L, Jr Pyelitis glandularis J Urol, **60**: 343, 1948

[2] Arey Developmental Anatomy Philadelphia, W B Saunders Co, 5th ed

Felix, W Cited by Arey

adhere to one another to form a lining while the cells of the mesoderm lie apart from one another. Because mesodermic cells in their early stage lie detached from one another, extremely anaplastic epithelial neoplasms of mesodermal origin may assume sarcomatous characteristics. Both entoderm and mesoderm participate in the development of the epithelium of the urogenital system. The digestive canal is formed from the entoderm and the caudal portion (cloaca) is destined to participate in the development of the bladder and urethra.

In the more lateral portion of the mesoderm small clefts develop and coalesce to form the coelomic cavity and the lining of this cavity is known as mesothelium. The medial portion of the mesoderm is known as mesenchyme, part of which, the nephrotome, is the anlage of a large portion of the urogenital system (fig. 2). The first set of kidneys, the pronephros, which develop from the nephrotome, contribute the pronephric ducts which reach the cloaca and open into it at approximately four weeks. When the pronephric tubules degenerate, the mesonephros appropriates the pronephric ducts which now become the mesonephric ducts (fig. 3). The third and final set of kidneys develop as buds from the posterior aspect of the inferior portion of the mesonephric ducts and these buds, the metanephric ducts, form the ureter, pelvis and collecting tubules of the kidney. The collecting tubules complete the formation of the mature nephron by connecting with the pre-formed mesenchymal convoluted tubules and glomeruli.

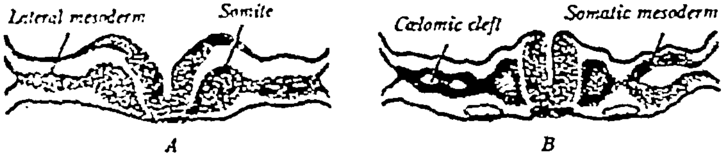


Fig. 218.—Origin of the human intra-embryonic cœlom, shown by transverse sections. × 65. The right half of each section is somewhat more advanced than the left. *A*, At two somites; *B*, at seven somites.

Fig. 1. From Arey's *Developmental Anatomy*, 5th ed. (Courtesy W. B. Saunders Co., publishers.)

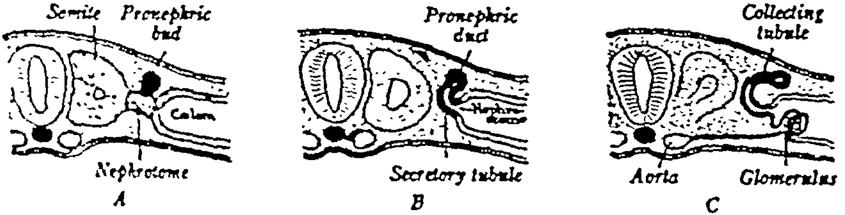


Fig. 234.—Development of the human pronephric tubule, illustrated by transverse sections of early embryos (semidiagrammatic). × about 140.

Fig. 2. From Arey's *Developmental Anatomy*, 5th ed. (Courtesy W. B. Saunders Co., publishers.)

During this 6 weeks of embryonal life the cloacal septum pushes caudad and divides the cloaca into a bladder and rectum. The metanephric ducts (ureters) revolve about the mesonephric ducts to occupy positions on the anterior aspect. As the bladder enlarges, the lower part of the mesonephric ducts and part of the metanephric ducts become incorporated into the floor of the bladder and that portion of the cloaca which is destined to become the posterior urethra (fig. 4). At completion of this process and with the formation of the posterior urethra by ventral closure, the mature bladder is formed into which the paired metanephric ducts (ureters) enter. The paired mesonephric ducts (ejaculatory) now open into the urethra. The bladder therefore has a dual origin, in part mesodermic and in part entodermic. The mucosa about the orifices of both the

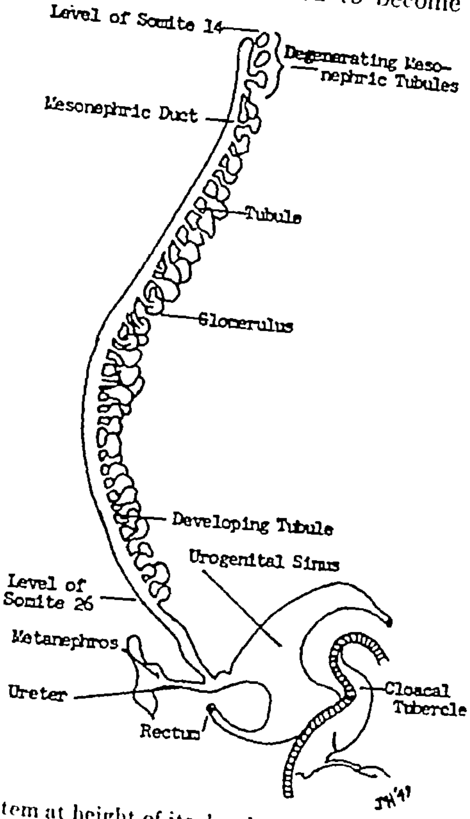


FIG. 3. Mesonephric system at height of its development. Arising from caudad extremity is metanephros. Copied from Arey's *Developmental Anatomy*, 2nd ed. (Prentiss, after Felix. Courtesy W. B. Saunders Co., publishers.)

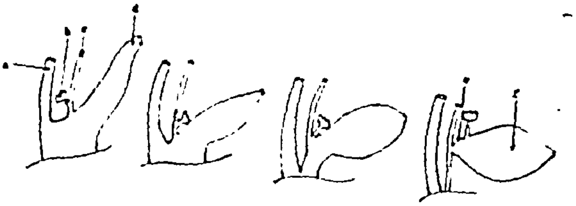


FIG. 4. Evolvement of trigone of urinary bladder in human embryo. *a*, Rectum; *b*, metanephros and metanephric duct; *c*, mesonephric duct; *d*, urachus; *e*, trigone; *f*, bladder.

paired ureters and ejaculatory ducts and of that portion of the bladder between is of mesodermal origin. The remainder of the bladder, hereafter spoken of as dome, which was originally part of the cloaca, is, as is the rectum, of entodermal origin. Similarly the floor of the urethra above the openings of the ejaculatory ducts is of mesodermic origin and the remainder of the internal urethra is of entodermic origin. A number of outgrowths from the mesodermic floor of the urethra form the male prostate.

Although the mesodermal origin of the prostate and trigonal epithelium is questioned, our observations support this belief. The mesonephric duct in the male becomes the vas deferens and epididymis while in the female only small vestiges remain in the form of Gärtner's ducts. It is well to recall that the secondary sex organs develop under the influence of the gonads. Genital organs develop in the embryo either from mesonephric ducts or from müllerian ducts according to the ascendency of male or female hormones and, at the same time, regression occurs in the opposing structures. For the purpose of applying these facts to the variation in morphology of urinary bladder epithelium, we have studied 13 cases of cystic trigonitis, two cases of rectal mucosal ectopia of the dome, two cases of cystitis glandularis which involve both the trigone and the dome, one papillary adenoma of the dome of the bladder, four adenocarcinomas of the trigone simulating prostatic carcinoma, three adenocarcinomas of the dome which simulated intestinal carcinoma and one case of carcinoma sarcomatodes of the trigone of the bladder, and in addition, one case of reversionary metamorphosis of urethral mucosa to a rectal type. Changes in the normal epithelium of the bladder may be classified on a basis of metaplasia, cataplasia or ectopia.

METAPLASIA

Metaplasia is the transformation of one type of tissue into a related type and is caused by alteration of function or a change of environment. In the presence of urinary stagnation, precipitation and calculus formation, together with irritation, the stratified transitional epithelium of any portion of the bladder may change to the more protective squamous type which may even keratinize (epidermal metaplasia or so-called leukoplakia). This type of metaplasia may also occur in vitamin A deficiency. Because carcinomas more commonly arise in bladders which have been subjected to irritation, squamous cell carcinomas are frequent in contradistinction to the relatively benign transitional cell papilloma. Under irritative influences the transitional epithelium may also undergo glandular metaplasia. Glandular metaplasia of the normal epithelium would most likely develop in that portion of the epithelium which possesses this potentiality, that is, the trigone. It has been our experience that cystitis cystica or glandularis is frequently limited to the trigone of the bladder and is similar to urethritis, ureteritis and pyelitis cystica. In our series of 17 cases of cystitis glandularis, the condition was limited to the trigone in 13 instances. It is possible, too, that glandular metaplasia may also result from hormonal imbalance. Prostatic hypertrophy which is due to a proliferation of new formed urethral glands is also probably due to hormonal imbalance. Therefore the same hormonal imbalance which causes hypertrophy of the prostate may be a contributory cause to the development of cystic trigonitis. It is interesting to note that 12 of our 13 patients were males and all were above the age of 37. The one female was 60 years of age. If the above outlined hypothesis is correct, it would be expected that the epithelium of the glands in cystic trigonitis would be similar in histologic characteristics to that of the prostate. In the development of the cysts there is an invagination of the transitional epithelium and the top layer of infolded stratified transitional epithelium becomes columnar with basilar placed nuclei and finely granular eosinophilic cytoplasm (fig. 5). As the glands continue to grow the stratified transitional epithelium gives way to a single layer of columnar epithelium which is capable of secreting mucus but does not form goblet cells (fig. 6).

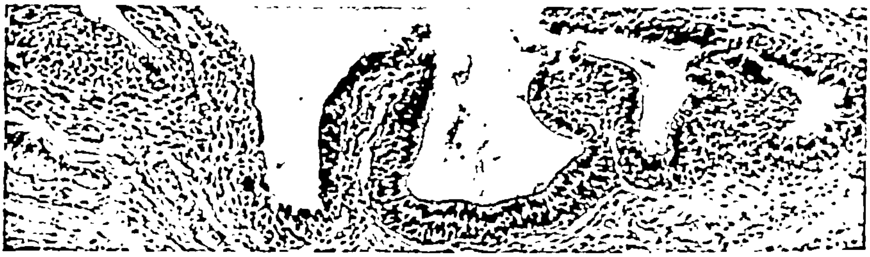


FIG. 5. Cystitis cystica, early stage. Upper layer of lining epithelium is columnar in type, and presents granular cytoplasm and elongated nuclei.

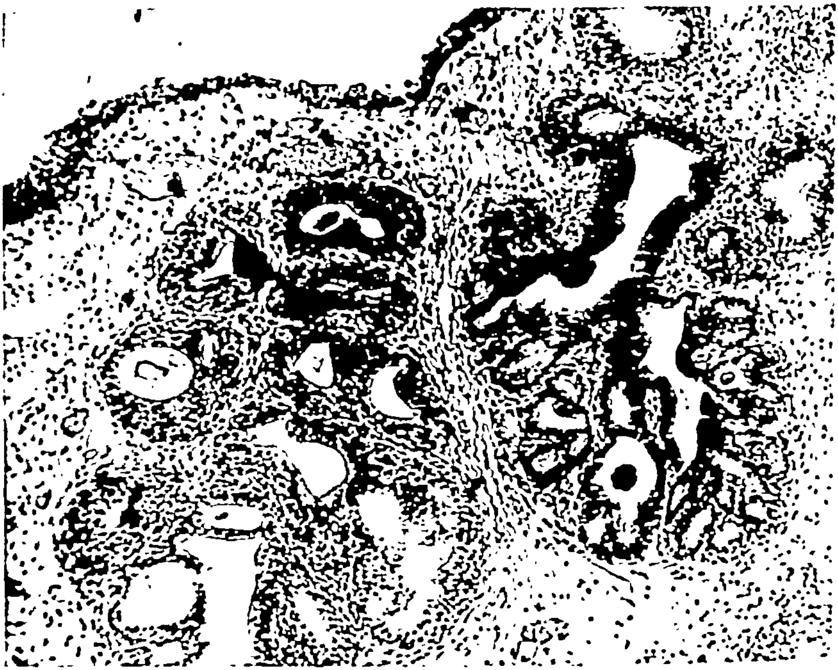


FIG. 6. Negro aged 29 Rounded mass at bladder trigone and extending to dome. Cystitis glandularis Glands are lined with columnar epithelium similar in characteristics to that of prostate This change occurs in area of wolffian duct origin, trigone.

ECTOPIA AND CATAPLASIA

Ectopia may be defined as misplaced epithelial remnants of a previous stage of development. Because the dome of the bladder is a derivative of the hind gut and is of entodermic origin, nests of rectal glands may occasionally be found (fig. 7). The epithelial structure is entirely different from the glands of the trigone and strikingly resembles the surface and glandular epithelium of the large intestine. The cytoplasm is clear, goblet cells are abundant and the small pyknotic nuclei are situated in the extreme basal portion of the cells It should be noted that in our two cases with ectopic rectal mucosa the lesions were found only in the dome of the bladder (entodermic derivative). It is also known that frequently in exstrophy of the bladder much of the mucosa resembles that of the rectum. This arrested development of the mucosa probably results from failure of development of the functional activity of the mucosa because the bladder does not assume the role of a reservoir. When epithelium loses its normal function, it may revert to a type through which it has passed in its previous development. This is known as reversionary metamorphosis or cataplasia. In a patient with a stricture of the bulbous urethra, several sinuses and fistulas developed. Most of these became epithelialized with stratified squamous epithelium (metaplasia). However at the site of the stricture, a granulating sinus developed which became epithelialized with an epithelium strongly resembling rectal mucosa (fig. 8) (cataplasia). Further support of our belief that cystitis glandularis may assume

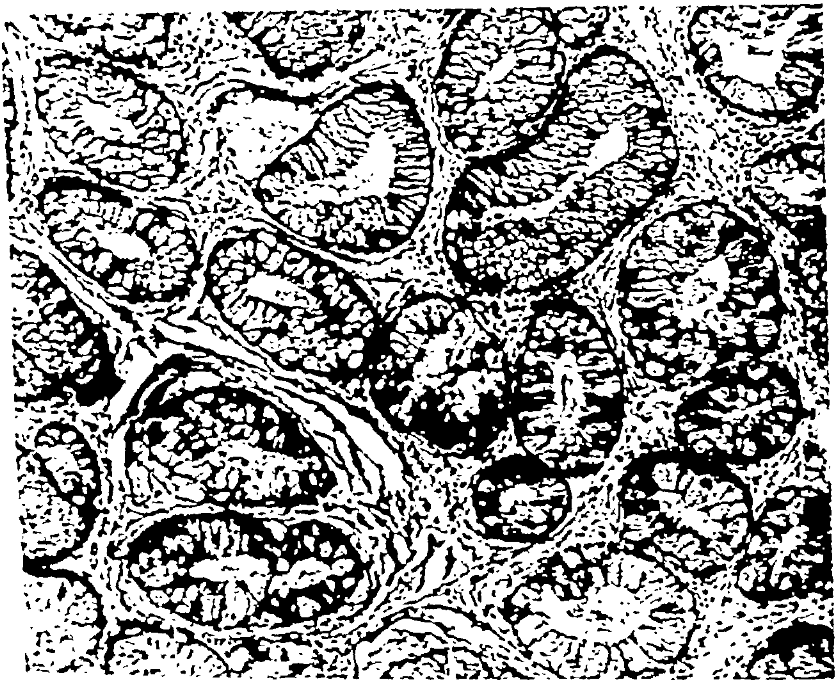


Fig. 7. Same case as figure 6. Cystitis glandularis. Large goblet cells with clear cytoplasm and flattened basilar placed nuclei are similar to cells of rectal glands. This type of gland may be found in dome of bladder which is derived from entoderm.

two different histologic forms, according to the site of development, is presented in 2 cases where the lesions of the bladder were noted as cystic tumor masses located at the boundary of the trigone and the dome. Histologic study of these two masses revealed both types of glands, those resembling the urethral and prostatic glands and those resembling the rectal type of glands. Because, in both instances there was a rather sharp delimitation between the two kinds of glands, it must be assumed that the prostatic type arose from that part of the tumor mass which encroached upon the trigone, whereas the rectal glandular tissue arose from the adjacent epithelium of the dome (figs. 6 and 7).

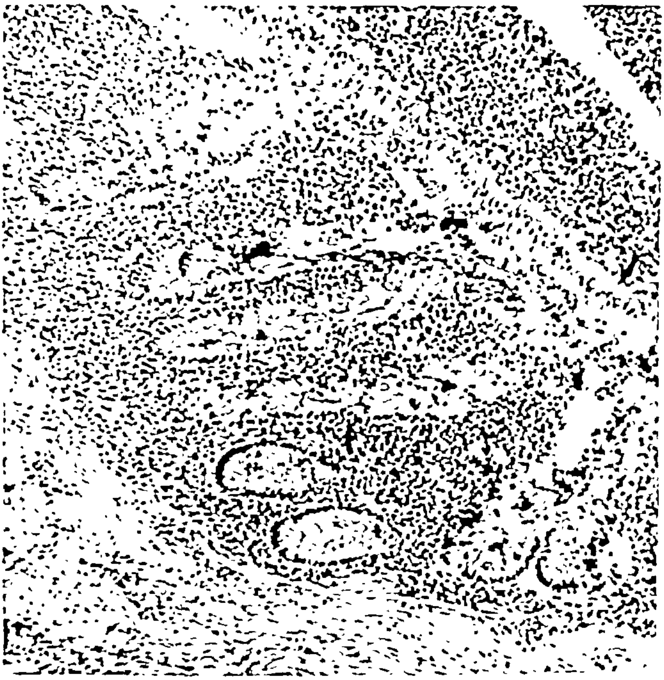


FIG. 8. Sinus of membranous urethra. Note goblet cells in epithelium lining tracts distal to ejaculatory ducts.

CYTOGENESIS OF NEOPLASMS

The usual benign neoplasm of the bladder is a papilloma. In benign tumors the epithelium is similar to that of the structure from which it arises. Therefore most of the papillomas are of stratified transitional epithelial type. However, because of possible ectopia or perhaps reversionary metamorphosis, benign papillary adenomas of the intestinal epithelial type may arise from the dome of the bladder. We have observed one such case where a small mucosal tumor situated 1.5 cm. above the left ureteral orifice was removed and presented a histologic picture similar to a polypoid adenoma of the rectum.

The variation in the pattern of malignant tumors of the bladder can also be explained from the previous presentation. Carcinomas most frequently arise in bladders which have been subjected to irritation. Irritation leads to metaplasia which is usually of the squamous type. The most common carcinoma of the

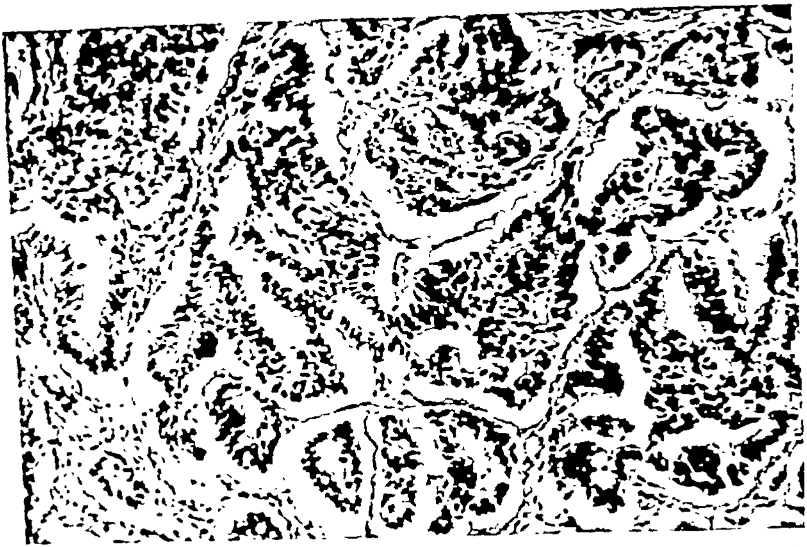
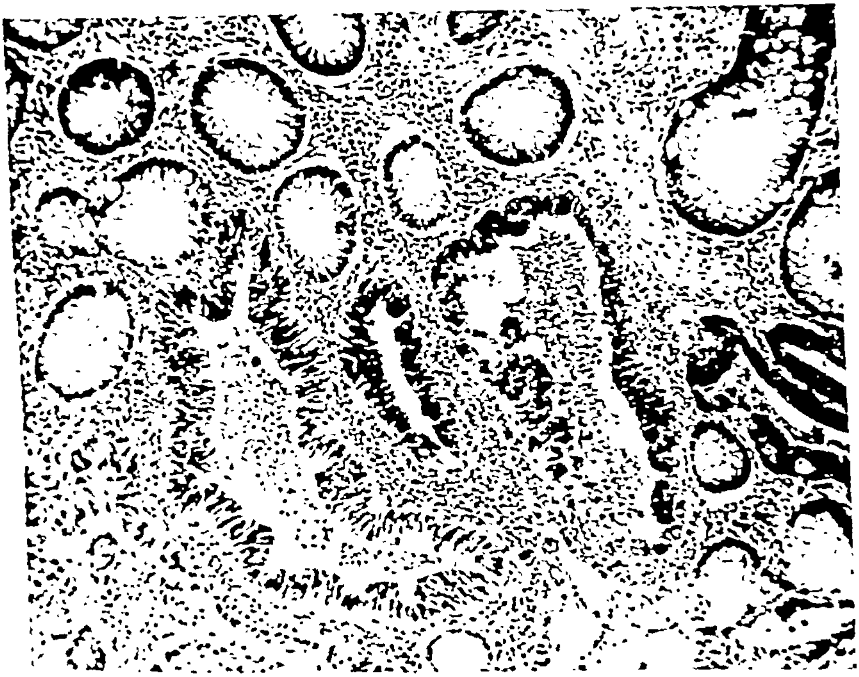


FIG. 9. Adenocarcinoma of urinary bladder trigone. The histologic characteristics are identical to those of adenocarcinoma of prostate.



the bladder which resembled those of the prostate, it was found that these arose from the trigone (fig. 9); three of these were in males, aged 59, 61 and 65 years, and one from a female, aged 63. The predominance of males and the late age incidence may reflect the possible role played by male hormone imbalance. It is known that in adenocarcinoma of the prostate some benefit is derived from

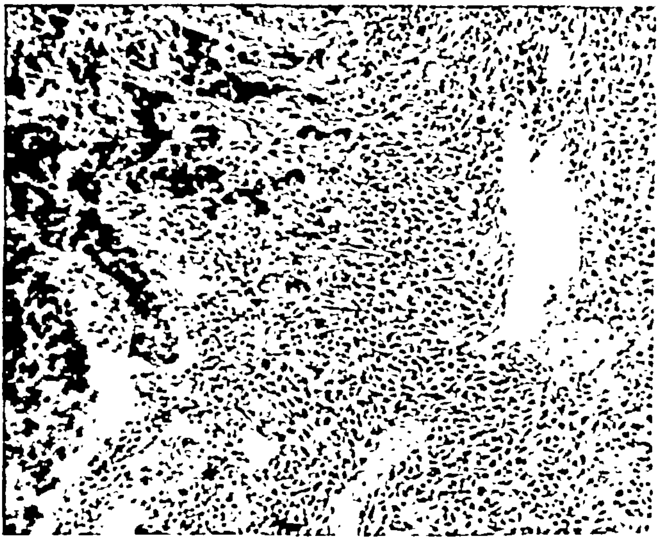


Fig. 11. Sarcomatoid carcinoma of urinary bladder trigone. Transition from epithelial carcinoma cells to small round cells of sarcoma is imperceptible.

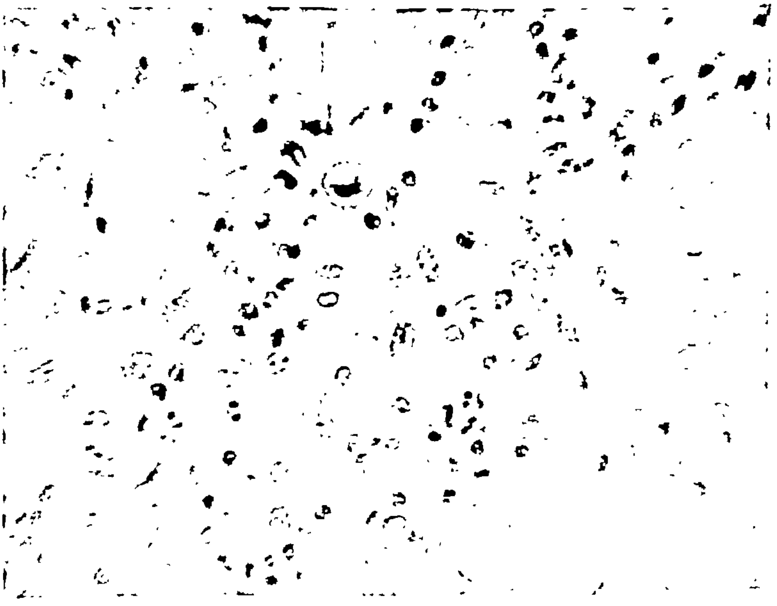


Fig. 12 High power photomicrograph of an area of transition taken from figure 11.

estrogen therapy or castration. With this in mind it is reasonable to suppose that medical or surgical castration might have a favorable effect in adenocarcinomas which develop from that portion of the bladder in which the epithelium is of wolffian duct origin. This finds support in the observation of Shivers and of Lich and Grant.[3]

Adenocarcinomas similar to those of rectal origin may also be anticipated in the bladder. These may arise from ectopic rests of rectal mucosa or may represent a reversionary metamorphosis, that is, reversion to an earlier stage of embryonic development. Because the dome of the bladder is of entodermic origin, this would be the logical site of such neoplasms. The three adenocarcinomas of the dome of the bladder which we have observed all possessed the histologic characteristics of carcinomas of the digestive tract, that is, deep branching glands, tall columnar epithelium with elongated nuclei, tendency to stratification of the nuclei and the presence of goblet cells (fig. 10).

In the early embryo the primitive mesoderm is composed of cells which do not adhere to one another and therefore are not of the lining type. However, from these cells lining tissue does develop, such as is found in derivatives from müllerian and wolffian ducts. Oncology recapitulates ontogeny in a reverse manner and, when anaplasia is extreme, mesodermal epithelial neoplasms may revert to a sarcomatous structure. Sarcomatoid carcinomas and sarcomas of epithelial origin may therefore arise in the trigone of the bladder. We have observed one instance of such a case. At autopsy on a 70 year old Negress, a large necrotic mass was found in the trigone of the bladder. The architecture of the neoplasm contained both carcinomatous and sarcomatous elements with a gradual transition of one to the other (figs. 11 and 12). The observation of this case lends further support to the hypothesis that the epithelium of the trigone of the bladder is of mesodermal origin.

SUMMARY

The hypothesis of dual embryological (mesodermal and entodermal) origin of the urinary bladder is emphasized and the embryology of the bladder is reviewed.

The difference in the histologic picture of cystitis glandularis of the trigone and cystitis glandularis of the dome of the bladder supports this hypothesis.

Adenocarcinomas of the trigone of the bladder may resemble adenocarcinomas of the prostate, while the adenocarcinomas of the dome of the bladder may resemble adenocarcinomas of the colon.

Carcinoma sarcomatodes may arise from the trigone of the bladder because of its origin from mesoderm.

Correlation between the effects of hormonal therapy in malignancy of the bladder and the embryologic origin of the tissue from which the malignancy arises is suggested.

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[2] Shivers, C. H. de T.: Bilateral orchiectomy in advanced or recurring carcinoma of the prostate with severe subjective symptoms. J. Urol., 54: 530, 1945.

[3] Lich, R. and Grant, O.: Use of estrogens in the treatment of bladder tumors. J. Urol., 59: 1, 1948.

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ON THE OCCURRENCE OF LYMPHOID TISSUE IN THE URINARY ORGANS*

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Among the rare and interesting pathological conditions that occur in the urinary tract are the so-called proliferative lesions, characterized by the presence of lymphoid tissue.

It is generally believed that these lesions are of rather infrequent occurrence as evidenced by the few published articles on this subject. Cystitis follicularis occurs more frequently than does pyelitis follicularis and it has received more consideration in the literature. Schlomovitz wrote that in the routine examination of several thousand urinary bladders at autopsy, cystitis follicularis was very rarely seen. Stirling and Ash state that "the incidence of proliferative lesions in the bladder is much higher than the literature would indicate. Cystitis glandularis and especially cystitis follicularis are common findings in the material submitted to the Bladder Tumor Registry."

Hinman and Cordonnier reported 5 cases of cystitis follicularis, Pedroso recorded 1 case, and Stirling and Ash reported 4 cases.

Pyelitis follicularis is of rare occurrence. Stirling in 1939 reported that only 11 cases are on record. In the majority of cases, the condition is found at autopsy or when the kidney has been removed surgically for one reason or another.

This paper is based on a series of 32 cases of proliferative lesions of the urinary tract that were encountered on my service and the service of my colleagues at Presbyterian Hospital. Some of my cases are reported in detail because they presented interesting problems.

CASE REPORTS

Case 1. Mrs. M. D., aged 58, referred by the late Dr. D. E. Murphy, was admitted to the Presbyterian Hospital, May 15, 1938. One year ago she had painful and frequent urination, both day and night, associated with severe urgency. She gave no history of hematuria.

Physical examination was negative. The blood count was normal. Urinalysis showed: albumin 0; sugar 0; pus +; Red blood cells ++. A culture of the urine showed B. coli. Blood chemistry: nonprotein nitrogen 27.25 mg. per cent; urea nitrogen 9.2 mg. per cent; creatinine 1.4 mg. per cent.

X-rays and retrograde pyelograms were normal.

Cystoscopic examination May 18, 1938 under ethylene anesthesia showed that the mucous membrane of the bladder was red, velvety, and swollen. In the dome was seen an area about ¾ inches in diameter, which had the appearance of being composed of small isolated nodules. A similar area was seen on the base and another on the posterior wall. Several pieces were removed with the cystoscopic rongeur for diagnosis.

Urine from the right and the left kidney was free of pus, negative on Gram

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Read at annual meeting, Western Section, American Urological Association, Sun Valley, Idaho, June 26, 1951.

* Robert V. Day Lecture.

† Deceased

stain and sterile on culture. Smears for tubercle bacilli and guinea pig tests were negative.

At the time of the first cystoscopic examination a "tentative diagnosis" of carcinoma of the bladder was made. However, examination of the pieces of tissue removed with the cystoscopic rongeur showed "cystitis follicularis."

The patient was discharged on May 21, 1938, with an indwelling catheter.

The second admission was July 13, 1938. The indwelling catheter was removed at the end of 4 weeks. After the removal of the catheter, there was a prompt return of symptoms. She was advised to have a suprapubic cystostomy and surgical diathermy of the areas of cystitis follicularis.

Suprapubic cystostomy on July 18, 1938. Three distinct areas of cystitis follicularis were seen: one in the dome of the bladder, one on the posterior wall, and two nodules on the floor of the bladder. One area was excised. The remaining nodules were treated with surgical diathermy.

Histological examination of the excised nodule showed cystitis follicularis, which verified the diagnosis made on the biopsy specimen.

The patient was discharged on August 30, 1938 with a draining suprapubic sinus and marked urinary distress. She subsequently re-entered the hospital and was operated upon by Dr. V. C. David for acute cholecystitis. At this time she still had a good deal of bladder distress.

Case 2. Mrs. H. B., aged 41, referred by the late Dr. Karl Snyder, was admitted to the Presbyterian Hospital August 8, 1926. She had 3 children, living and well. She complained of hematuria, frequency of urination with severe straining, burning in the bladder, and itching in the vagina. She first noticed blood in her urine 3 years ago. The patient stated that about once a day she had blood in her urine and passed small clots. Frequency had been present for 3 years. The sensation of straining was noticed for only 3 months. This she described as a "desire to pass more urine than the bladder contained." The itching and burning in the vagina had been present about 2 years.

Physical examination was negative. Blood count: Red blood cells 4,360,000; white blood cells 11,100; hemoglobin 84 per cent. Blood pressure 102/64. Urinalysis showed albumin 4+; sugar 0; blood+; and an occasional leukocyte. A culture of the urine showed hemolytic streptococci. Many smears for the tubercle bacilli were negative. Three guinea pigs inoculated with bladder urine were negative for evidence of tuberculosis.

Cystoscopic examination on August 10, 1926 showed a white necrotic mass extending completely around neck of bladder with some involvement of the trigone. "A tentative diagnosis" of carcinoma was made and operation advised.

Suprapubic cystotomy was done August 12, 1926 under ethylene anesthesia. Around the internal urethral orifice, in the region of the left ureteral orifice, and extending to right ureteral orifice, was seen an ulcerated area which bled easily. A piece was removed for histological study. The ulcerated area was treated by surgical diathermy. Microscopic diagnosis: Cystitis follicularis; granular cystitis.

The patient was discharged September 16, 1926, free of symptoms.

Case 3. Mr. A. B., aged 19, was admitted to Presbyterian Hospital February

23, 1939. Subsequent admissions were on December 18, 1939, March 31, 1940 and July 15, 1940. The previous history was negative. The symptoms began 8 years ago with blood in urine. The attacks of hematuria lasted from 1 to 2 days. On several occasions, he passed clots. Nocturia, intermittent stream, terminal dysuria, and perineal pain had been present for 8 years. Great urgency had been present for four years.

Physical examination was negative. Urinalysis: albumin 1+; blood 4+; white blood cells 750 per c.mm. Urine culture sterile. Blood count: red blood cells 3,000,000; white blood cells 5,200; hemoglobin 74 per cent; blood pressure 106/85; Kahn test negative.

Rectal examination showed a *moderate enlargement of the prostate*. Residual urine 100 cc. Plain x-rays and excretory urograms were negative. The cystogram showed a diverticulum of bladder and filling defect on left side of bladder. Electrocardiogram showed left axis deviation.

Cystoscopic examination showed the presence of a necrotic papillary tumor on left lateral wall of bladder and the opening of a diverticulum on the right lateral wall and some enlargement of the prostate.

February 25, 1937, transurethral resection of the bladder tumor and fulguration of the base; resection of the prostate.

Pathological diagnosis: Epidermoid carcinoma of the urinary bladder; cystitis follicularis; benign hyperplasia of prostate gland.

Subsequent admissions were for fulguration of bladder tumors.

The last cystoscopic examination was negative. The last report from his physician stated that the patient was well and free of symptoms.

Case 4. Mr. N. P., aged 78, was admitted to the Presbyterian Hospital October 21, 1949 and discharged November 14, 1949. The previous history was negative. The present illness began 7 years ago with frequency of urination both day and night, difficulty in starting the stream, dribbling, burning, and decrease in the size of the stream.

A few moist crepitant rales were present at both bases. Blood pressure 220/80; blood count was normal. Urinalysis showed albumin 0; sugar 0; blood 0; few pus cells. Urine culture: Streptococcus hemolyticus+++, Staphylococcus aureus 1+. Non protein nitrogen 35 mg. per cent.

Rectal examination revealed a smooth, symmetrical enlargement (3 plus) of the prostate.

An x-ray of the chest showed some increase in lung markings at both bases suggestive of asthmatic changes, scoliosis of spine and calcification of the aorta. An electrocardiogram showed left auricular strain; auricular premature beats. Plain x-ray and excretory urograms were negative.

Transurethral resection was done under pentothal sodium. Because of the huge size of the prostate it was decided to do a two-stage resection. The first resection was performed October 29, 1949; the second resection was done on November 7, 1949. Pathological diagnosis (Dr. George Hass): Benign prostatic hypertrophy; cystitis follicularis; cystitis cystica.

The patient was discharged free of symptoms on November 14, 1949.

Case 5. Mr. O. C. A., aged 58, was first admitted to Presbyterian Hospital September 18, 1939. At 20 years he had a chancre. He was treated with pills, injections in the arm and injections in the hip. Bed wetting had been present for 15 years; some slight daytime incontinence; some hesitation for 10 years, slow stream for 10 years.

On physical examination knee jerks were absent. Romberg sign, patient fell to the left. No Babinski. The pupils did not react to light. The external genitalia were negative. Rectal examination showed slightly enlarged prostate. Massage of the prostate equaled pus 4+. Residual urine 1550 cc. Blood chemistry and blood count were normal. Wassermann and Kahn tests were negative. Blood pressure 140. The diagnosis of tabes dorsalis was verified by Dr. Avery.

Transurethral resection of prostate September 27, 1939. Pathological diagnosis was chronic prostatitis and cystitis follicularis.

Case 6. Mr. F. J. P., aged 67, was admitted to the Presbyterian Hospital January 9, 1950; he was discharged January 13, 1950.

The patient had three previous transurethral resections. His present complaint was frequency of urination and nocturia; during the night he was obliged to void 5 or 6 times.

Physical examination: Blood pressure 150/80. Some edema of ankles. Rectal examination negative. X-ray and excretory urograms were negative. Blood count and blood chemistry were normal.

Transurethral resection January 10, 1950 under pentothal nitrous oxide anesthesia. Two small adenomatous nodules were seen on the floor of the prostatic urethra. Some thickening of the interureteric ligament, which was resected, as were the small nodules in the prostatic urethra.

Pathological diagnosis by Dr. George Hass: Benign prostatic hypertrophy; urethritis cystica; urethritis follicularis.

Case 7. Mr. L. B. I., aged 65, was admitted November 8, 1949; discharged November 18, 1949. The patient has been a "known diabetic" for 17 years. In 1947 I performed a transurethral resection for benign prostatic hypertrophy and resected a benign papilloma in his bladder. The patient entered the hospital on November 9, 1949 because of the presence of red blood cells which persisted in his urine on repeated examinations. He had no urinary symptoms. Rectal examination was negative. Blood count showed red blood cells 3,320,000; white blood cells 6,900. Urine: sugar 1+; albumin 0; casts 0. Nonprotein nitrogen 23 mg. per cent. Culture showed B. coli. Kahn test negative. An electrocardiogram showed possible old posterior infarct.

Cystoscopic examination on November 10, 1949 revealed a small papilloma on the right side of the bladder. This was treated by fulguration. A few nodules of prostatic tissue were resected.

Pathological diagnosis by Dr. George M. Hass: Benign prostatic hypertrophy; acute and chronic cystitis, cystitis follicularis; chronic inflammation and fibrosis of prostate, transitional metaplasia of prostatic ducts, acute and chronic inflammation of prostatic ducts.

Case 8. Mr. A. W., aged 71, was admitted to Presbyterian Hospital on April

12, 1950 and discharged May 10, 1950. The patient had had two transurethral resections, the last one performed five years ago, since which time he had been very comfortable. He complained of the presence of gross blood in the urine with the passage of clots. There was some urgency and frequency of urination, and on admission he was obliged to void four to five times a night.

Physical examination was negative. Blood pressure 240/120. Blood count was normal. Urinalysis: gross blood; albumin+; sugar 0. Red blood cells microscopically 4+, and chemical for blood 4+. Nonprotein nitrogen 35 mg. per cent. Kahn test negative.

X-rays and excretory urograms were negative. Cystoscopic examination April 19, 1950 showed no sign of tumor to explain the gross bleeding. Rectal examination showed 1 plus enlargement of prostate.

Suprapubic prostatectomy on April 19, 1950 under pentothal sodium anesthesia: *A relatively large right lateral lobe and a somewhat smaller left lobe were* removed. There was no bleeding. The examination of the removed specimen showed patches of chronic infiltration characterized by the presence of large numbers of lymphocytes, plasma cells a few eosinophils, and rare polymorphonuclears. In some areas there was pseudo-follicular formation; they contained no recognizable germinal centers. A small amount of the mucosa of either the bladder or ureter was present and this epithelium revealed a stratified squamous epithelium.

Pathological diagnosis by Dr. George M. Hass: Prostatitis "pseudo-follicularis"; squamous metaplasia of the bladder mucosa.

Case 9. Mr. B. J. S., aged 58, entered the Presbyterian Hospital on March 5, 1950. In 1926 he had an exploratory laparotomy followed by peritonitis, abscess formation and a subsequent brain abscess.

In 1932 a diagnosis of ulcer of the duodenum was made.

In 1940 suppurative orchitis developed and the testicle was removed.

The patient had had a knowledge of stones in his right kidney for 12 years. He had suffered with acute attacks of severe pain in the right kidney region, associated with chills and fever. The attacks were increasing both in severity and frequency. He recently developed polyuria, polydipsia and a greatly increased appetite.

On physical examination the head and neck were negative. The liver was palpable below the costal arch. Examination of his stool was positive for blood.

Blood pressure 110/70. Hemoglobin 14 grams. Blood examination: red blood cells 4,000,000 per c.mm.; white blood cells 5,600 per c.mm.

Urinalysis: albumin 2+; sugar++. Occasional granular cast. Urine contained 1,580 pus cells per c.mm. Culture showed Bacillus pyocyaneus, Staphylococcus albus and Streptococcus anhemolyticus. Nonprotein nitrogen 49 mg. per cent.

X-rays showed an area of increased density over the left kidney pelvis. The left excretory urogram showed dilatation and clubbing of the calyces. The right excretory urogram was normal.

The patient was placed on diabetic management before the operation was performed. Nephrectomy was done on March 10, 1950.

Pathological diagnosis by Dr. George M. Hass: 1) An infected type of hydronephrosis with subacute pyelitis and subacute perinephritis; 2) presence of extensive acute and chronic pyelonephritis; 3) severe arteriosclerosis with the presence of a few nephrosclerotic infarcts associated with it; 4) presence of tiny adenoma of tubular origin. The epithelium of the kidney pelvis had undergone squamous metaplasia. Many lymph follicles were seen in the mucous membrane of the kidney pelvis. These contained well defined germinal centers. Pyelitis follicularis.

The stone removed showed calcium oxalate and calcium phosphate.

Case 10. Mr. O. B., aged 85, was admitted to the Presbyterian Hospital on July 5, 1950. Two years ago the patient had a transurethral resection for benign prostatic hypertrophy, from which he made an uneventful convalescence. On admission his only complaints were the presence of blood in the urine and burning in the urethra. These symptoms began two weeks ago. The bleeding occurred at the beginning of urination. He had passed a few small clots.

Physical examination was essentially negative. Blood pressure 150/80. Hemoglobin 12.5 grams. Blood examination: red blood cells 4,000,000 per c.mm.; white blood cells 6,000 per c.mm. Blood chemistry: nonprotein nitrogen 36 mg. per cent.

Urinalysis: specific gravity 1.010. Albumin 1+. Microscopic examination showed three or four red blood cells per high power field. Culture of urine showed Bacillus pyocyaneus. X-rays and excretory urograms were normal.

Cystoscopic examination showed the presence of several large adenomatous nodules of prostatic tissue around the internal urethral orifice and in the prostatic urethra. These nodules were covered with large blood vessels and bled easily.

Transurethral resection of prostate was done July 7, 1950. Fifteen grams of tissue were removed. Bleeding was well controlled. Pathological diagnosis (Dr. George M. Hass): Benign prostatic hypertrophy with acute and chronic inflammation and necrosis; severe squamous metaplasia of urethral epithelium; urethritis follicularis.

The patient was discharged on July 11, 1950.

ETIOLOGY

The cause of these proliferative lesions is still unknown. No doubt the same factors are responsible for their presence immediately gives rise to the question of whether or not lymphoid tissue is a normal constituent of the urinary tract.

There are a good many differences of opinion on this subject and for purposes of discussion they may be presented under the following four headings:

1) Some authors believe that lymphoid tissue is a normal constituent of the bladder. (Stöhr, Böhm and Davidoff, Bailey, S. Alexander, Weichselbaum, Ziegler, Aschoff, and T. Cajigas.)

2) Another group maintains that lymphoid tissue is not a normal constituent of the urinary bladder. (Piersol, Stoerck, and J. C. Boileau Grant.)

3) A third group is of the opinion that the mucous membrane of the bladder does not normally contain lymphoid tissue, and that when lymphoid tissue is

found, its origin is attributed to chronic catarrh of the mucous membrane, or to a pathologically altered mucosa. (Chiari, Przewoski, Schlomobitz, Hinman, Ewing, E. E. Smith and W. M. Copenhaver.)

4) Hinman and Cordonnier state "there may be a wide individual variation in the amount of lymphoid tissue present in the normal bladder. When a relatively large amount of lymphoid tissue is present, due to stimulation as the result of chronic infection, hyperplasia occurs which then presents a picture of cystitis follicularis. In cases in which there is little or no lymphatic tissue, however, the same amount of infection over the same period produces only the findings of chronic cystitis."

Zuckerkandl described two types of cystitis follicularis: the true and the false. In the true type the lymph follicles were rounded, the peripheral cells being closely crowded together in rows, with typical germinal centers. In the false type, or, as it is sometimes called, cystitis pseudofollicularis, the germinal centers were not found, and the cellular arrangement was widely distributed. Palisading of cells at the periphery was not observed. Stirling and Ash consider these as simple states in the development of a lymphatic follicle.

Stirling and Ash state that the follicular type of cystitis frequently develops in any prolonged infection of the bladder. They further state: "It is our opinion, based on the clinical cases in this record, and on the large amount of material in the Bladder Tumor Registry, that follicular cystitis, or at least the development of lymphatic follicles is a very common occurrence in a diseased bladder, whether it be from inflammation or from tumor, and that these follicles have no significant relationship to tumor."

Other factors that have been mentioned as a cause are syphilis, typhoid, gonorrhea, tuberculosis, stone, and stricture.

The colon bacillus was found in the urine from the bladder in the majority of the cases reported in the literature. However, infection with the B. coli alone is not the causative factor because of the relative frequency of this type of infection as compared with the infrequency of cystitis follicularis and pyelitis follicularis.

In the cases which are reported in this paper, culture of the urine showed a variety of organisms, among which were B. coli, hemolytic streptococci, Streptococcus anhemolyticus, Staphylococcus aureus, and B. pyocyaneus.

Interesting in this connection is the report by Greene and Feldman of cystitis follicularis in an adult female dog. The authors reasoned that any of the etiologic agents advanced by the various writers bear only an incidental relationship to cystitis follicularis. Syphilis, gonorrhea and typhoid fever are not known to occur in the dog; hence, none of these diseases can be the etiologic factors in the cases which they report.

SYMPTOMS

The symptoms are generally due to the underlying pathological condition, such as benign prostatic hypertrophy, papilloma, carcinoma or stone. In the cases of cystitis follicularis there may be hematuria, dysuria, frequency, burning on urination, urgency, and nocturia. There may be pain over the bladder.

In the cases of pyelitis follicularis, the primary disease overshadows the picture. The symptoms are due to calculi, pyelonephritis, tuberculosis or severe hydronephrosis.

CYSTOSCOPIC APPEARANCE

In cases of cystitis follicularis the condition has been mistaken for carcinoma as occurred in two of my cases. Stirling and Ash state that in cystitis follicularis, the mucosa of the bladder is covered with nodules of varying size, rather closely packed together, and of a grayish-red color. They resemble Peyer's patches in the intestine. These masses are firm on pressure.

Their findings are in accord with mine.

The biopsy specimen of any suspicious mass or nodule in the bladder should be submitted for analysis.

TREATMENT

There is no specific treatment for this condition. Foci of infection when present should be eradicated on general principles. Stone, tumor, or benign prostatic obstruction when present should receive appropriate treatment. The treatment must be directed to the primary underlying pathological condition as mentioned previously.

When no underlying pathological change is present, as was the case in two of my female patients, suprapubic cystostomy and fulguration should be carried out.

Pyelitis follicularis is generally found after a kidney has been removed for stone, severe infection, tuberculosis or hydronephrosis.

SUMMARY

Thirty-two cases of proliferative lesions of the urinary tract are reported, viz. 15 cases of cystitis follicularis; 5 cases of pyelitis follicularis; 6 cases of prostatitis follicularis; 4 cases of urethritis follicularis; 1 case of nephritis follicularis; and 1 case of perinephritis follicularis.

Twenty-three cases occurred in males and nine in females.

The age groups were as follows: 20–29, 2 cases; 30–39, 2 cases; 40–49, 2 cases; 50–59, 10 cases; 60–69, 7 cases; 70–79, 8 cases; 80–89, 1 case.

Of the 15 cases of cystitis follicularis the preoperative diagnosis was benign hypertrophy of prostate in 7 cases; adenocarcinoma of prostate in 2 cases; carcinoma of bladder in 3 cases; papilloma of bladder in 1 case; contracted neck of bladder in one case; contraction of the internal urethral orifice in one case.

Of the 5 cases of pyelitis follicularis the preoperative diagnosis was renal calculi in 2 cases; renal tuberculosis in 1 case; and infected hydronephrosis in 2 cases. Of the 6 cases of prostatitis follicularis, the preoperative diagnosis was benign prostatic hypertrophy in 5 cases and cancer of prostate in one case. In the case of nephritis follicularis the preoperative diagnosis was renal calculi and chronic pyelonephritis. In the urethritis follicularis group, three had been diagnosed as benign prostatic hypertrophy, and 1 case of hemorrhagic cystitis.

Cystitis follicularis may be and has been mistaken for carcinoma of the bladder. Biopsy should be made of any suspicious mass in the bladder.

[illegible] S. Michigan Ave., Chicago 3, Ill.

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HISTOLOGICAL STUDY OF VESICAL UROTHELIUM INTERVENING BETWEEN GROSS NEOPLASMS IN TOTAL CYSTECTOMY

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The incidence of bladder tumor "recurrence" is high. More than one-third of patients with bladder tumors returned to the Squier Urological Clinic for additional biopsies (table 1). The figure is low because some patients had further treatments without repeat biopsies. Operative procedures have become more radical but a concomitant improvement in end-results has not occurred. Why? Why is there so great an incidence of bladder tumor "recurrence?"

There are three possible explanations:

1) The "recurrences" are *regrowths* due to inadequate surgery or fulguration, and/or

2) The "recurrences" result from "*seedings*" or "*implants*" prior to, during or after operative procedure, and/or

3) The "recurrences" are *new tumors* due to the continued action of an unknown *carcinogenic agent*.

A number of clinical and experimental observations favor each of the foregoing explanations:

"REGROWTH"

It is obvious that any incompletely removed tumor will continue to grow. It has been shown that benign tar papillomas of a rabbit's ear grow rapidly and become invasive (malignant) following *partial* destruction.[1] Inadequate fulguration of a papillary vesical tumor has often resulted in activation and expansion of the remnants.

"SEEDING" OR "IMPLANT"

a) The frequent association of bladder tumors with those of the pelvis and ureter may be due to "seedings" from above. When the involved side of the upper urinary tract is removed then bladder "recurrences" are apt to cease.[2]

b) The occasional development of tumor nodules in a suprapubic scar following cystostomy for tumor is strongly suggestive of "implant" or "seeding" of neoplastic cells.

c) A recent experience gives a vivid demonstration of the potency of cell-implants. A 56-year old man underwent nephro-ureterectomy for ureteral tumor, and at the same time a similar urothelial growth of his urinary bladder was ablated by the suprapubic route. At the end of the operation a bilateral vasoligation was done, without change of instruments or glove. Within 7 months a nodule developed at the very site of the right vasoligation. It was suspected of being an inflammatory mass, but the biopsy revealed a urothelial carcinoma of a

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Read at annual meeting, American Urological Association, Chicago, Ill., May 11, 1951.

[1] Yamagiwa, K. and Ichikawa, K.: J. Cancer Research, 3: 1, 1918.

[2] [illegible], M. M.: J. Urol., 65: 2[illegible]5, 1951.

cell-pattern identical with that in the bladder and ureter (fig. 1). That cells of a carcinoma can easily be implanted was illustrated by the report of such an occurrence in the donor area of a skin graft.[3,a]

It is noteworthy that bladder tumors are enclosed within a hollow viscus which contracts and can compress its relatively normal mucosa against the neoplastic mass. It has been shown that tumor cells of the squamous cell variety are more easily separable than normal cells.[3,b] The shedding of cells from a urothelial neoplasm is probably a frequent occurrence. Cell desquamation is the basis for tumor cell search in urine. It is conceivable, therefore, that seeding can occur before, during or after operation. Innumerable cells are probably shed but fortunately only rarely do any 'take hold', perhaps on or in an injured or denuded or hemorrhagic site.

TABLE 1

Total number of cases: 1,083
No. of cases with 1 biopsy: 739
No. of cases with more than 1 biopsy: 344

No. Biopsies	1	2	3	4	5	6	7	8	9	10	11	13
No. Cases	739	186	80	35	17	12	7	1	2	1	2	1

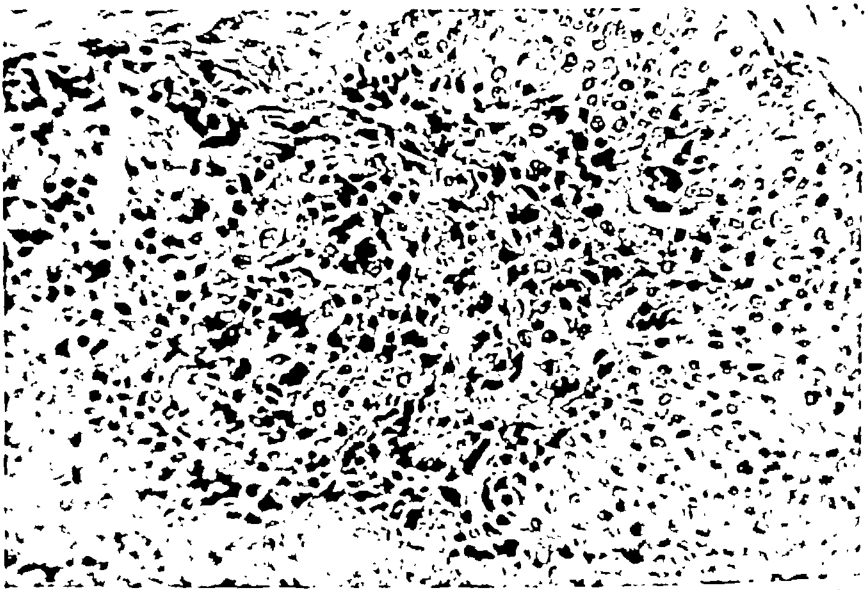

FIG. 1. Path. No. 10179. Implant along vas deferens. Patient had cystostomy and fulguration of bladder tumor. Vasoligation and resection were performed at end of operation. Several months later nodule developed on one side, in region of scar.

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[a] Brandes, W. W., White, W. C. and Sutton, J. B.: Surg., Gynec. & Obst., 82: 212, 194
[b] Comman, D. R.: Cancer Research, 4: 625, 1944

“NEW TUMOR(S)”

a) The association of pelvic and/or ureteral neoplasms with those of the bladder may also be used as an example of the manifestation of some unknown carcinogenic agent.

b) The spontaneous retrogression or disappearance of bladder neoplasms following bilateral ureteral transplants suggests that the diversion of urine containing a carcinogenic agent may have had that beneficial effect.[4]

c) The presence of a carcinogenic factor in the butyl alcohol extract of human urine is of interest.[5] The demonstration of tumorigenic decomposition products from the urine of patients with *nonoccupational* cancer of the bladder is significant.[6]

d) Some of the aniline dyes exert specific carcinogenic effects on vulnerable sites in the urothelium of vulnerable individuals. Examples:

- i) Beta-naphthylamine can induce bladder tumor formation.[7–11]
- ii) Beta-anthraquinoline can induce kidney tumors.[12]
- iii) Bladder tumors have been induced in inbred strains of mice by means of 2-acetylaminofluorene,[13] and by means of the Horning technique[14] methylcholanthrene, acting on the mucosa of mice bladders, induced transplantable bladder carcinoma.[15, 16]

e) In schistosomiasis of the urinary bladder the excretory products of the parasites may contain a carcinogenic agent.

f) The biologic course of nonoccupational vesical neoplasms in the human suggests the presence in the urine of some unknown carcinogenic agent or agents with varying specificity and intensity of action. The site of predilection in the human; i.e. near ureteral orifices, trigone, bladder neck, etc.[17] as compared with the usual site in the four-footed animals (anterior wall) is also suggestive that the agent(s) is carried in the urine.

With the foregoing in mind we made a study of the *grossly normal-looking vesical urothelium of patients* with bladder tumors who had undergone total cystectomy. Our object was to determine whether the mucosae contained microscopic evidence of activity.

Procedure: Ten total cystectomy *tumor-bearing* bladders and five control

Wherever possible the latter were obtained on concentric circles extending 1.0, 2.0, 3.0 cm. etc. from the edges of the tumors:—

TABLE 3. *Epithelial tumors of urinary bladder (M. Melicow)*

Complex of carcinogen(s) acting on

Normal Urothelium

by Hyperplasia		by Metaplasia	
Simple thickening No stalks	Papillary Stalklet(s) Papilloma	In an Epithelial Direction *Squamous cell formation *Leukoplakia	In a Glandular Direction *Cystitis cystica *Cystitis glandularis ±mucin
by Anaplasia			
Carcinoma in situ	Papillary Ca Sessile Ca	Squamous Cell Ca	Adenocarcinoma ±mucin

* Occur also in chronic inflammation without neoplasm.

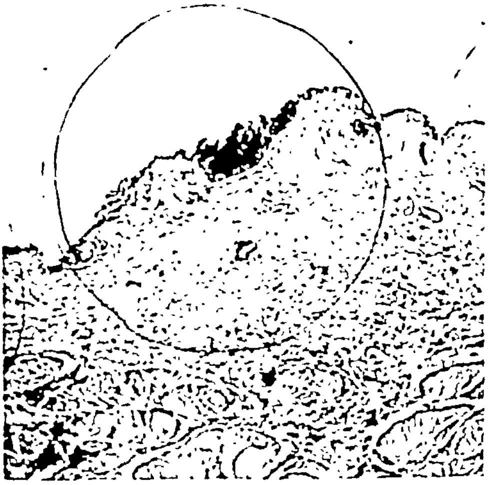

Fig. 2. Path. No 9869 Case 1. Focus of urothelial hyperplasia

FINDINGS

I. In tumor-bearing bladders

A. Changes in urothelium

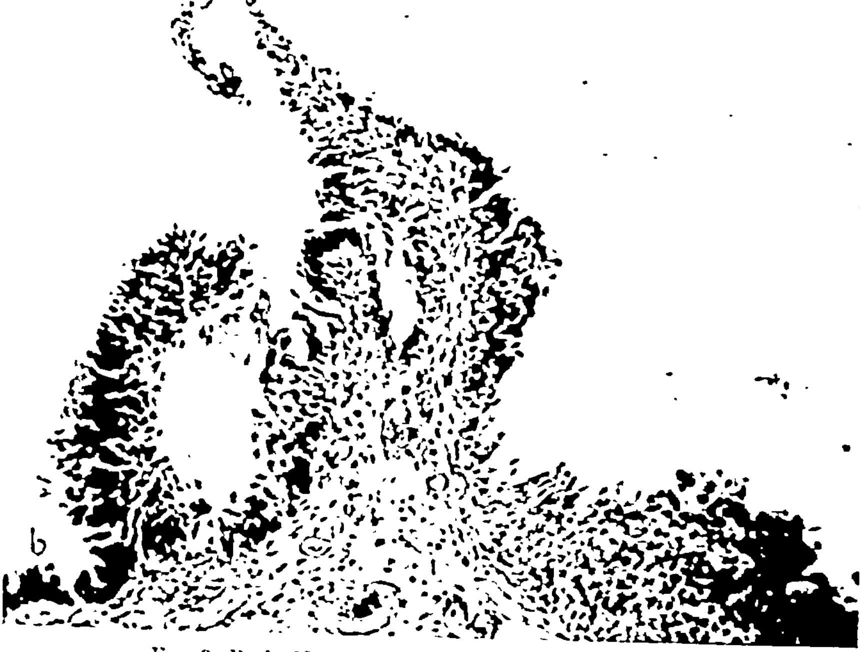

FIG. 3. Path. No. 9869. Case 1. Multiple "tongues"

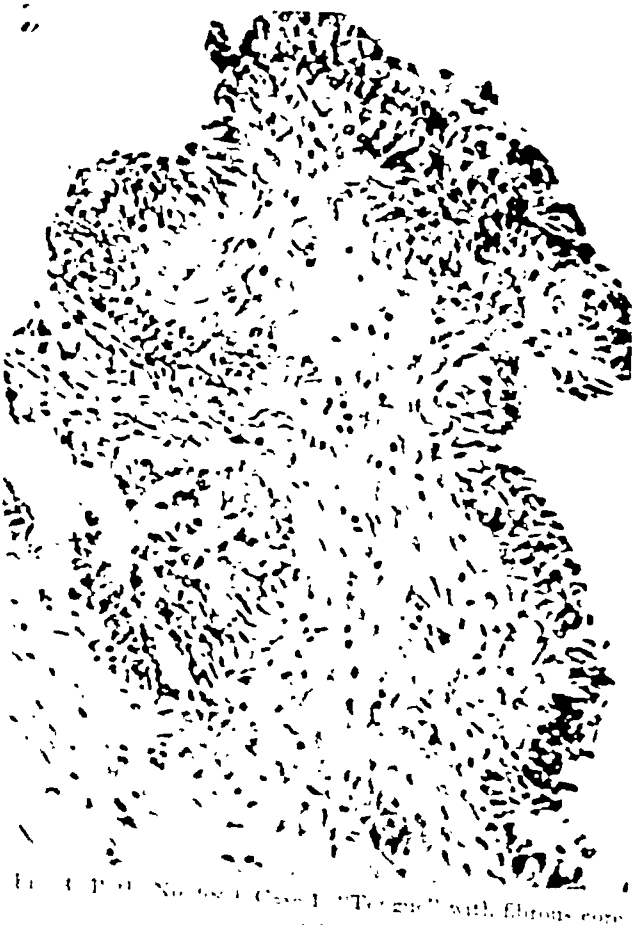

FIG. 4. Path. No. [illegible]. Case 1. "Tongue" with fibrous core

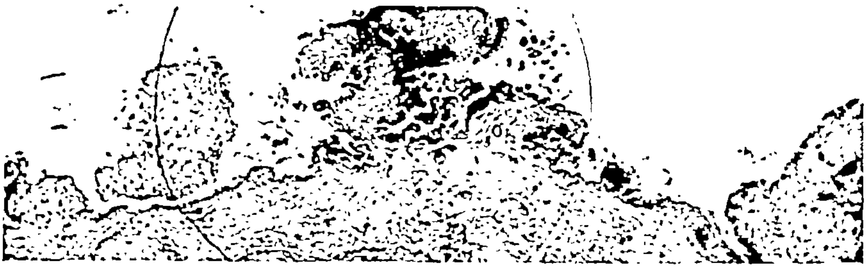

FIG. 5. Path No. 9854. Case 2. Multiple urothelial "tongues"

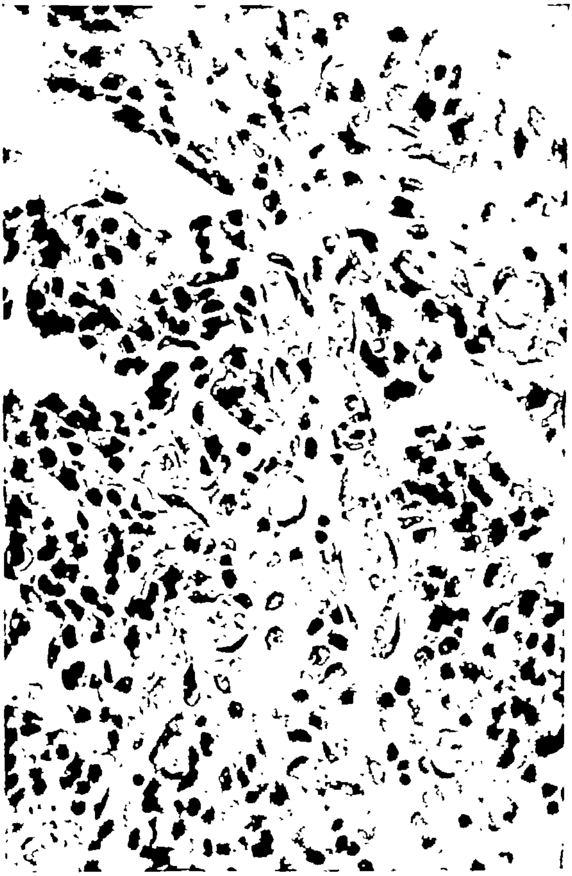

FIG. 6 Path. No 9854. Case 2. Urothelial "tongues" with vascular core

1) *Foci of hyperplasia without anaplasia*
   a) Simple thickening of urothelium (figs. 2, 9, 18)
   b) Urothelial "tongue", single or multiple,
      i) Composed of urothelial cells only (figs. 3, 5, 16)
      or ii) with vascular core (figs. 6, 10)
      or iii) with fibrous core. (fig. 4)

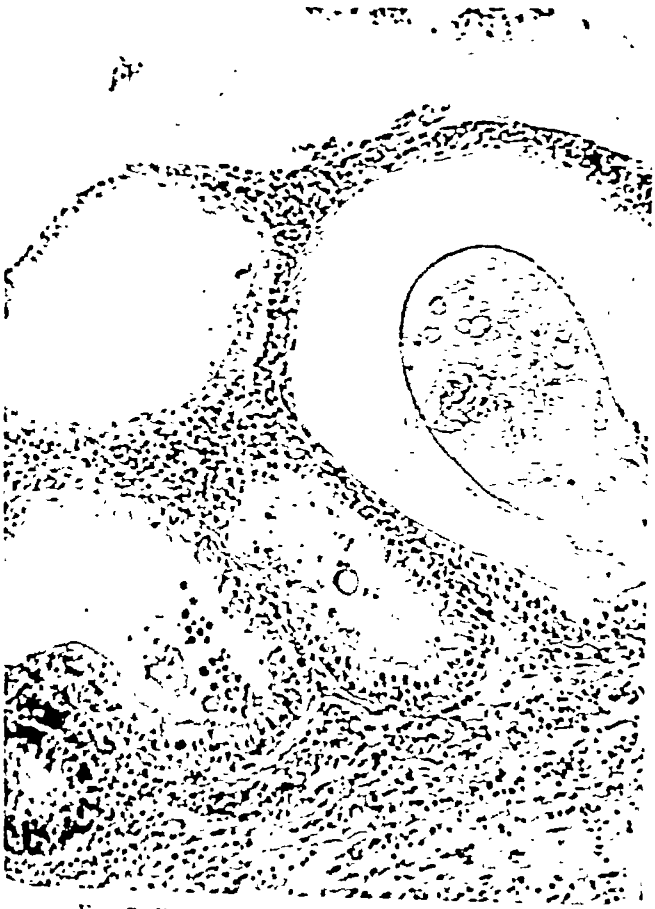

Fig. 7. Path. No. 9851. Case 2. Cystitis cystica

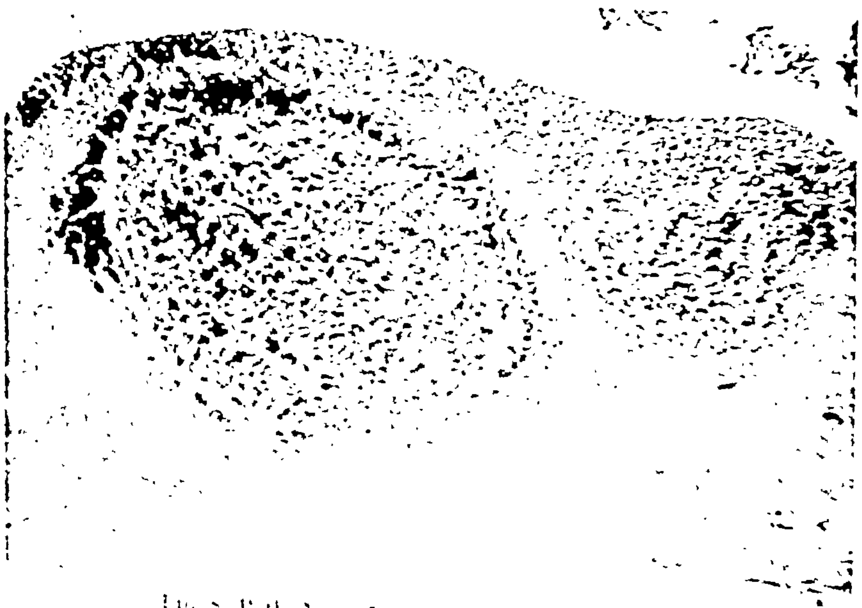

Fig. 8. Path. No. 9851. Case 2. Cystitis follicularis

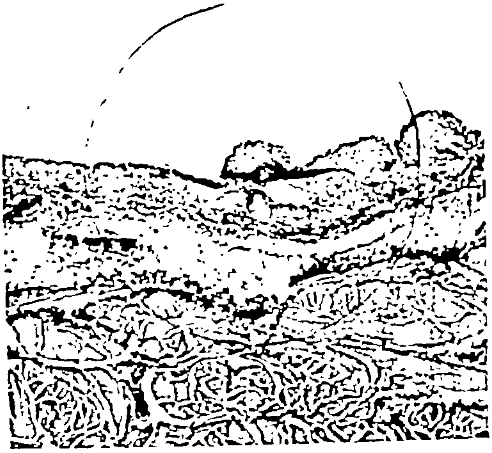

FIG. 9. Path. No. 10001. Case 6. Focus of urolithelial hyperplasia

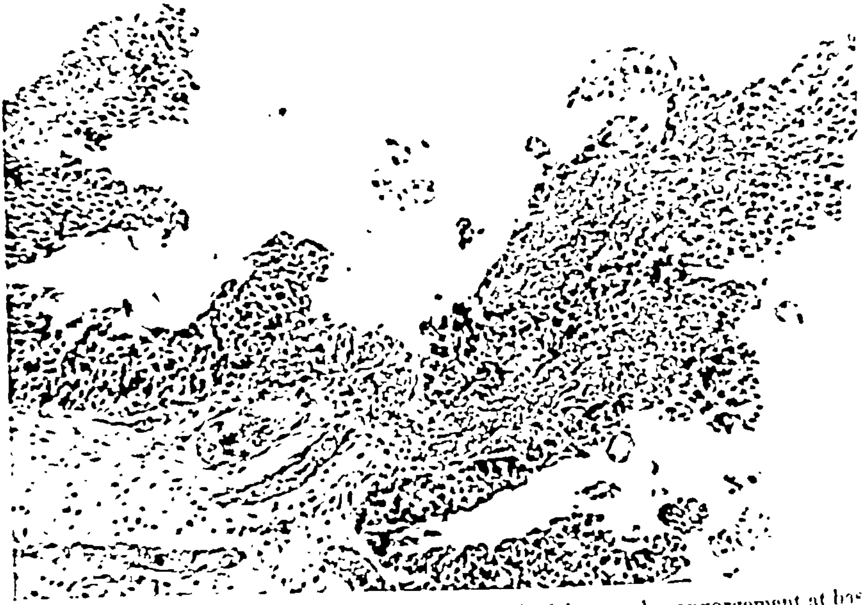

FIG. 10. Path. No. 10001. Case 6. Urothelial frond with vascular engorgement at base

2) *Foci of hyperplasia, with varying degrees of anaplasia*
   - a) Thickened urothelial layer with occasional hyperchromatism, giant nuclei (figs. 14, 17, 21, 25)
   - b) Similar change in "tongue" projections
   - c) *Intraurothelial carcinoma*, "carcinoma in situ" (figs. 15, 19, 20

3) *Foci of urothelial metaplasia*, usually in bladder which had several previous operations or fulgurations, or was infected or was the seat of a squamous cell tumor.

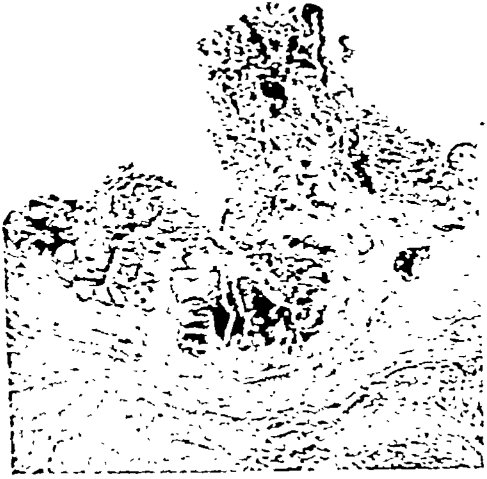

Fig. 11. Path. No. 10001. Case 6. Numerous fronds, cystitis cystica

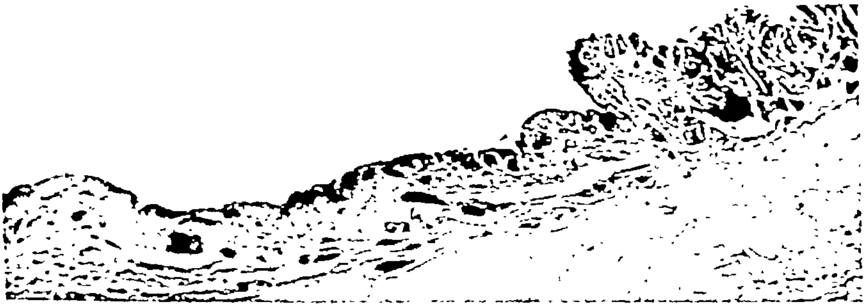

Fig. 12. Path. No. 10001. Case 6. Numerous cell nests

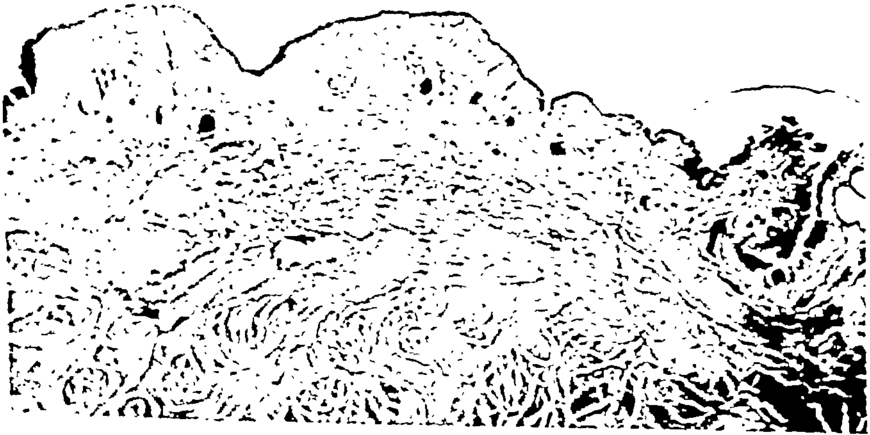

Fig. 13. Path. No. 10001. Case 6. Cystitis cystica

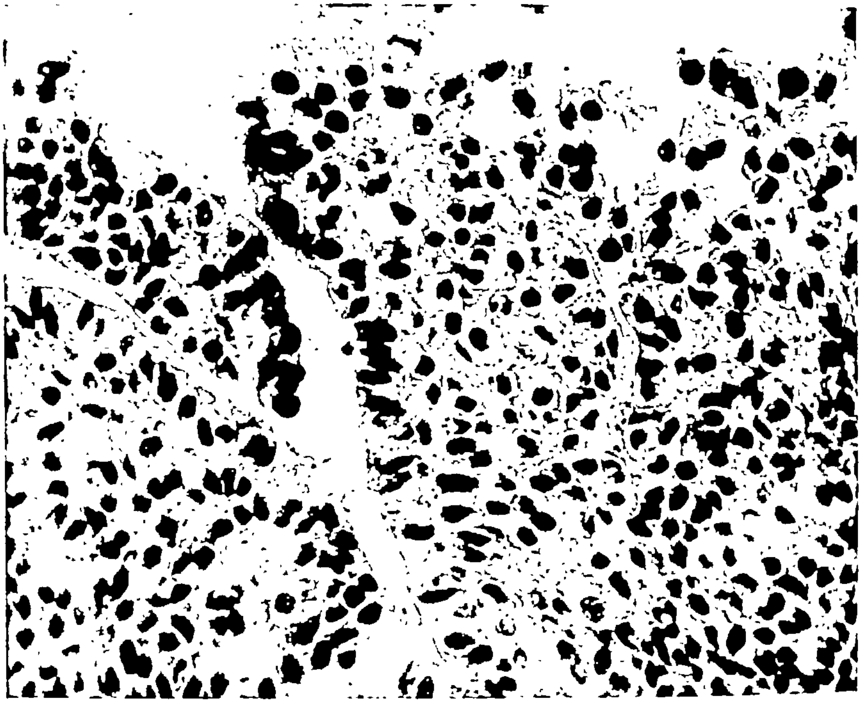

FIG. 14. Path. No. 10001. Case 6. Urothelial hyperplasia with nuclear hyperchromatism

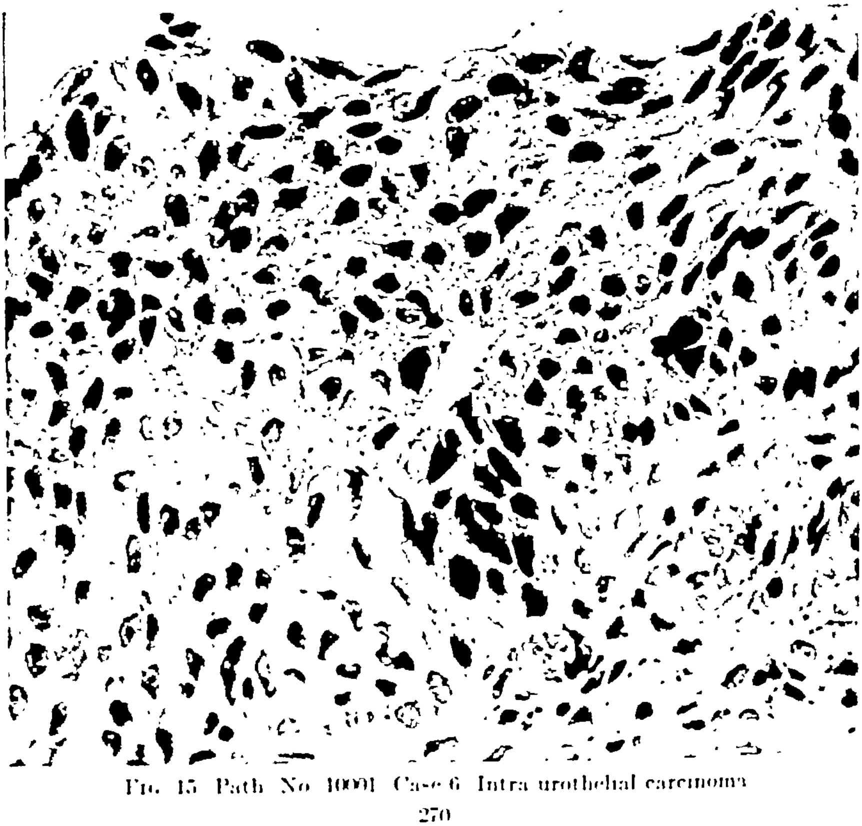

FIG. 15 Path No 10001 Case 6 Intra urothelial carcinoma

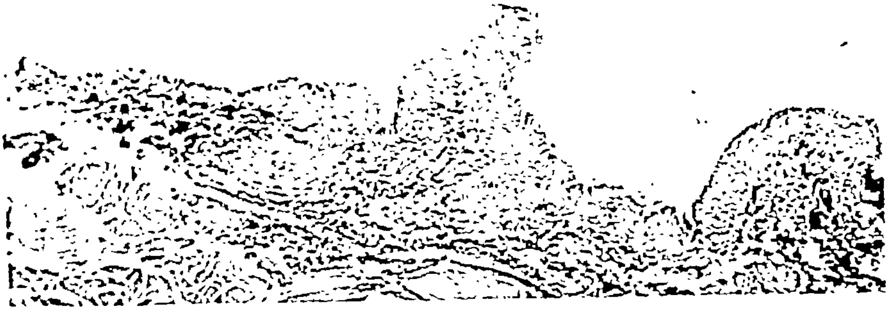

FIG. 16. Path. No. 10211. Case 7. Urothelial frond

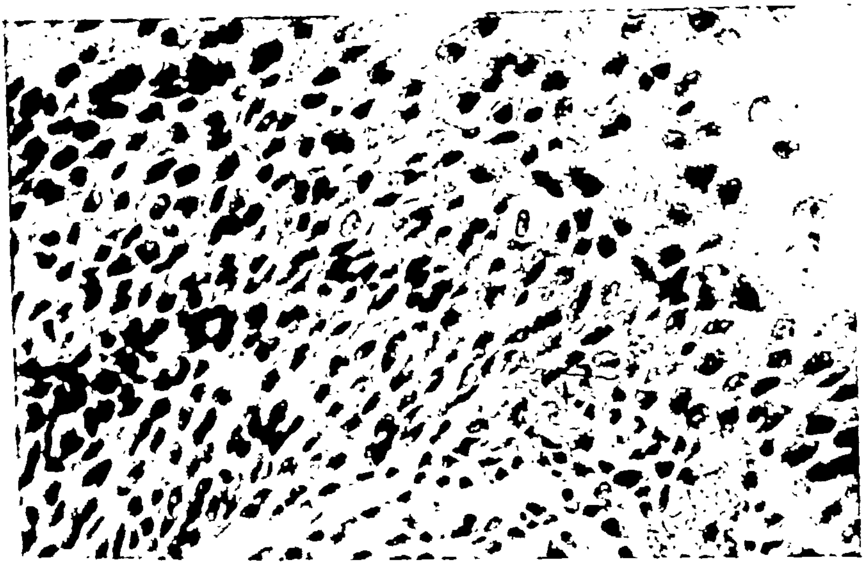

FIG. 17. Path. No. 10211. Case 7. Urothelial hyperplasia with nuclear hyperchromatism

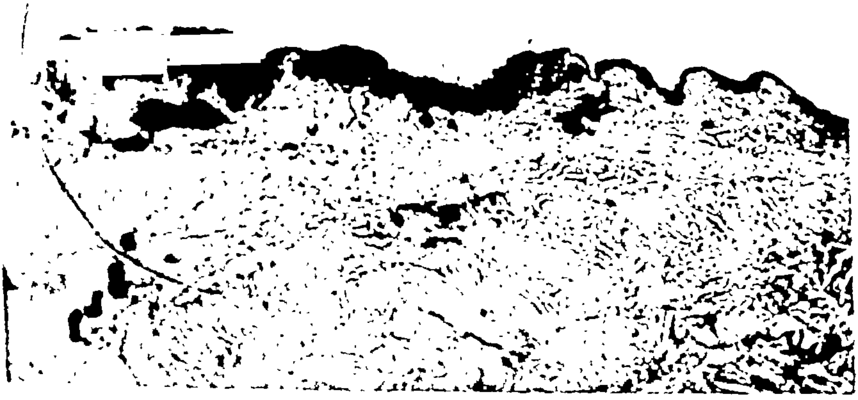

FIG. 18. Path. No. 8567. Case 9. Gradual increase in urothelial layers

a. Squamous cell metaplasia (figs. 21, 22)
b. Leukoplakia
c. Above with anaplasia; epithelioma in situ.
d. Above with cystitis cystica and glandularis (table 3)

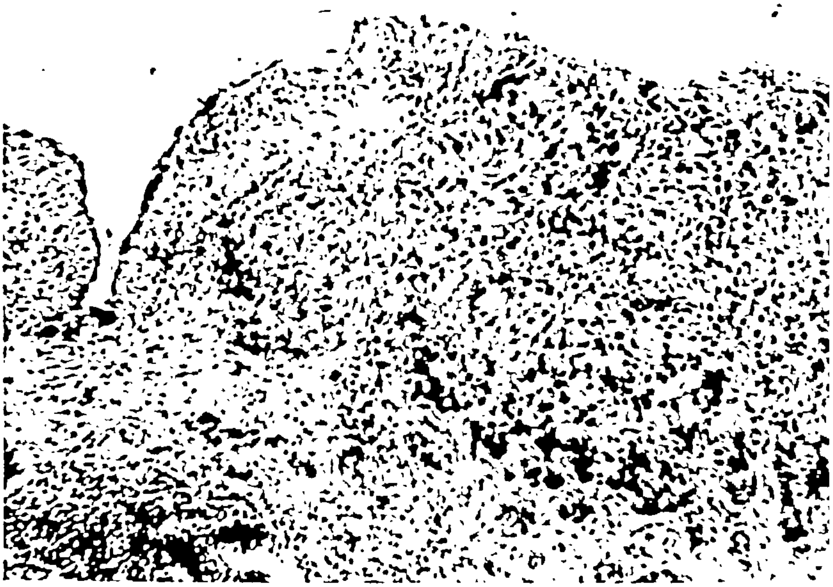

FIG. 19. Path. No. S207. Case 9. Intra-urothelial carcinoma

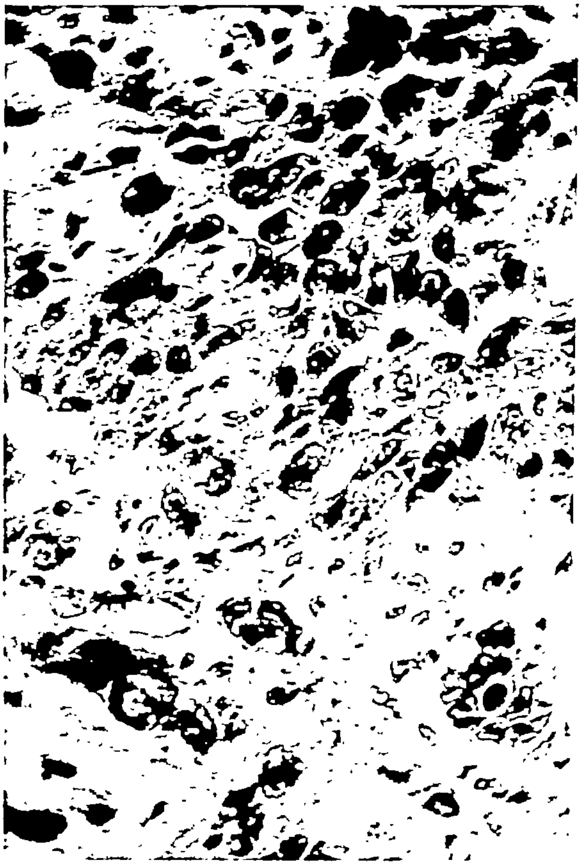

FIG. 20. Path. No. S207. Case 9. Intra-urothelial carcinoma

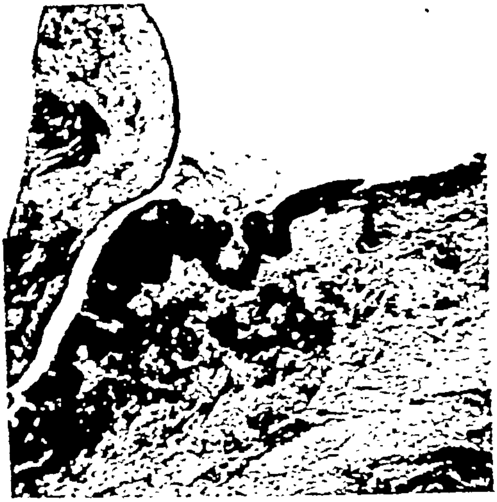

FIG. 21. Path. No. R119. Case 10. Areas showing squamous cell metaplasia

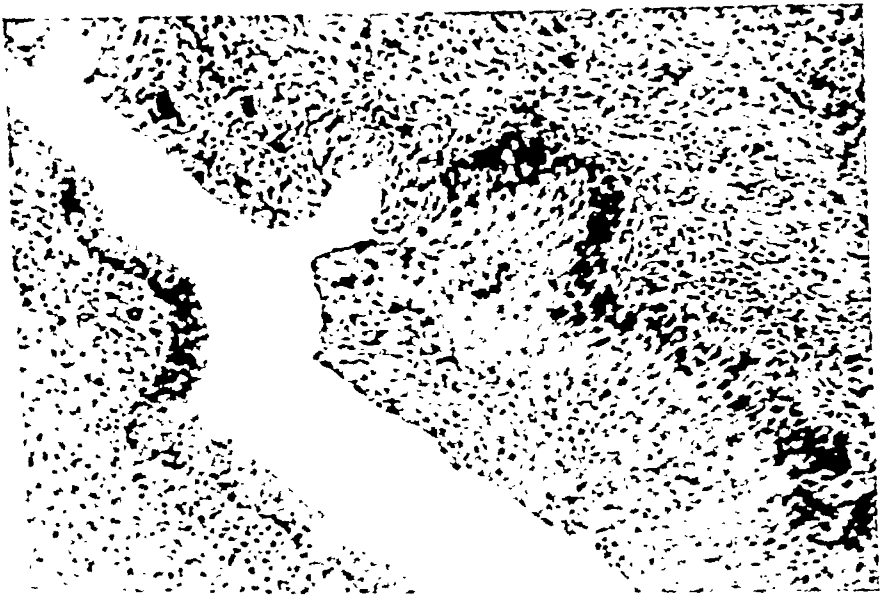

FIG. 22. Path. No. R119. Case 10. Areas showing squamous cell metaplasia

5) Miscellaneous findings:—
  a) Increase in *cell nests* (fig. 12)
  b) Multiple foci of *cystitis cystica* and *glandularis* (figs. 7, 11, 13)
  c) *Foci of ulceration*, in depths of some of which were clumps of malignant cells (seen particularly in an inflamed bladder in an area which lay in apposition with gross tumor during collapsed state of bladder, "seeding" via ulcer? (fig. 23)

B. Changes in submucosa and muscularis
  1. [illegible] [illegible] of [illegible]. Occasional extension to surface and into [illegible] (figs. 10 and 25)

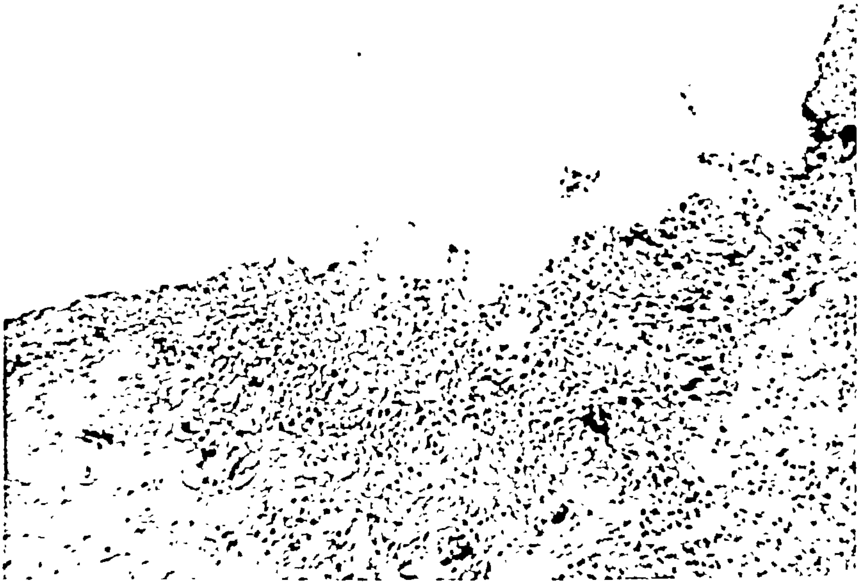

FIG. 23. Path. No. R119. Case 10. Surface ulceration with ? "explosive" invasion

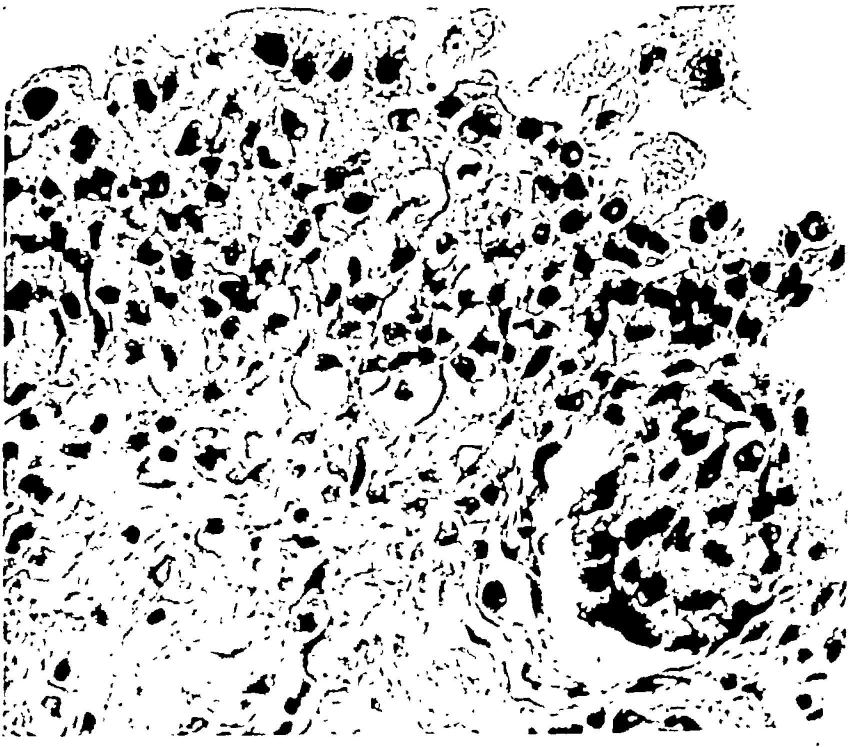

FIG. 24. Path. No. R119. Case 10. Hyperchromatism and some cell nest formation

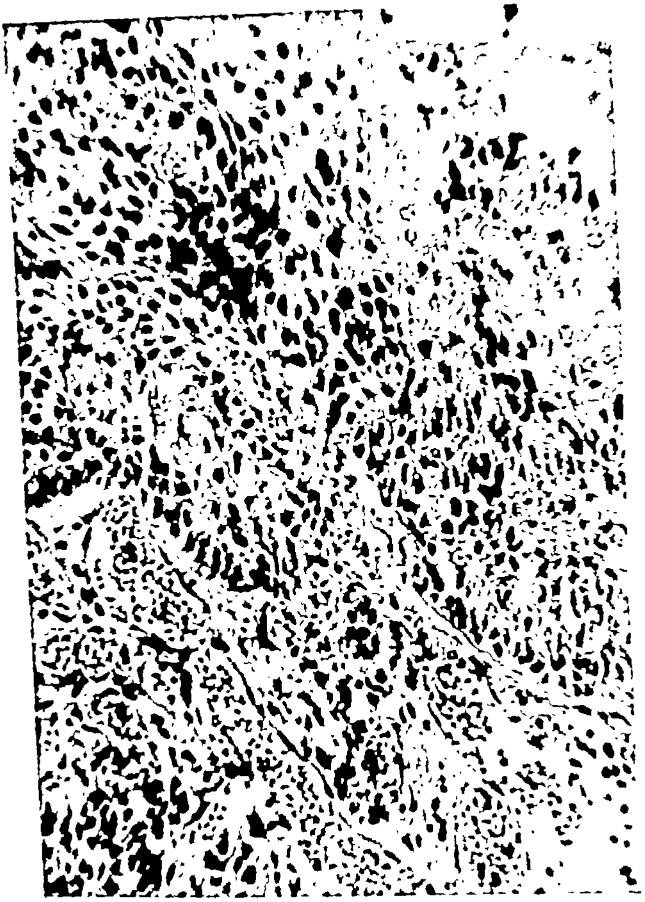

Fig. 25. Path. No. 1022, Case 8. Urothelial hyperplasia with nuclear hyperchromatism

2) Severe inflammation, particularly in multiple operations.
   a) Suppuration
   b) Cystitis follicularis (fig. 8)
   c) Interstitial cystitis
   d) Areas of necrosis
   e) Thrombosis of blood vessels, some with calcified plugs.

II. In *tumor-free* bladders (control)
   A. Changes in urothelium
      a. Rare foci of hyperplasia
      b. Cell rests present
      c. No Bowenoid changes
      d. Cystitis cystica and glandularis rare except in inflamed bladders
   B. Changes in submucosa and muscularis
      a. No significant lesions
      b. Cystitis follicularis in inflamed bladders

TABLE 2. *Study of grossly normal-looking mucosa of urinary bladders*

A. Tumor-bearing bladders

CASE NO. & NAME	PATH NO.	SEX	AGE	HISTORY IF PREV. TREAT.	OPERATION AND FINDINGS	DIAGNOSIS	FINDINGS IN GROSSLY NORMAL-LOOKING MUCOSA
1) L. B.	6669	M	57	*Terminal hematuria, 6 months*	*Total cystectomy. Bladder measured* 10 cm. in diameter Tumors on lateral walls. *Rt: 0.5 x 1.0 with thin* pedicle. Left sessile 1 cm. in diameter	*Anaplastic carcinoma of urinary* bladder, with signet ring formation, *invasion of muscularis and* blood vessels, Gr. IV	Urothelial hyperplasia (fig. 2), "tongue" formation some with fibrous stalks (figs. 3 and 4). *Cystitis* cystica and glandularis. Cell nests with hyperchromatism. Capillary engorgement
2) T. P.	6851	M	66	Recurrent hematuria. A number of previous cystoscopies and fulgurations. One treatment with radium	Total cystectomy: Posterior half of bladder floor and dome covered by papillary tumor with base which measured 3.5 cm. in diameter. Four small tumors nearby	Preponderantly differentiated papillary carcinoma of urinary bladder, Gr. II	Foci of urothelial hyperplasia,—some with vascular stalklets (figs. 5 and 6), cystitis cystica & glandularis (figs. 7 and 8)
3) B. H.	8151	F	63	*Recurrent hematuria, 8 years. Many* cystoscopies and fulgurations	*Total cystectomy: Bladder measured* 12 x 11 x 1.2 cm. Tumor involved floor and neck of bladder and measured 6 x 4 cm. another tumor 1 cm above 0.6 cm in diameter	*Completely anaplastic infiltrating* carcinoma of urinary bladder with invasion of muscularis, lymphatics and blood vessels	*Cystitis cystica and glandularis.* Foci of urothelial hyperplasia, "tongue" formation(s), squamous cell nests
4) H. I.	8260	M	53		Total cystectomy: Bladder measured 8.0 x 6.5 x 2.0 cm. Tumor occupied dome of bladder & measured 2.0 cm in diameter. A nodule 0.3 cm. in diameter is present nearby	Preponderantly anaplastic infiltrating carcinoma of urinary bladder with involvement of muscularis; Gr. IV	Foci of urothelial hyperplasia. No block serial done
5) D. S.	8629	M	68	Recurrent hematuria, 2 years. Many fulgurations, one via cystostomy	Total cystectomy: Bladder measured 10 x 7.5 x 2.5 cm. Studded with friable tumors, some with broad base	Well-differentiated, multiple papillary carcinomas of urinary bladder, Gr. II	Foci of urothelial hyperplasia. "tongue" formations, vascular finger-like projections

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Total cystectomy: Bladder meas[illegible] x 1.0 cm. Papillary [illegible] with base that [illegible] 2.5 x 1.0 cm. Sessile tu[illegible] 1.1 x 0.5 cm.	Partly differentiated (Gr. II) & partly anaplastic (Gr. IV) papillary carcinoma of urinary bladder	Foci of urothelial hyperplasia (figs. 9 and 14), numerous cell nest formations (fig. 12), "tongue" formations (figs. 10, 11 and 13), cystitis cystica and glandularis
[illegible]	[illegible]	M	[illegible]	Recurrent painless hematuria, 5 [illegible]. Several previous [illegible]	Total cystectomy: Nonpapillary tumor on [illegible] covering left ureteral orifice, base measured [illegible] cm. in diameter. Tumor 2.0 cm. high	Anaplastic infiltrating carcinoma of urinary bladder with invasion of muscularis, perivesical fat lymphatics and fascia, Gr. IV	Foci of urothelial hyperplasia (fig. 16), some with nuclear hyperchromatism (fig. 17)
M. A.	[illegible]	F	[illegible]	Recurrent hematuria, 17 years. Su[illegible] cystoscopies and fulgurations [illegible] open operation)	Total cystectomy: Tumor on floor base measures 8 cm.	Anaplastic infiltrating carcinoma of urinary bladder with spindle cell metaplasia and invasion of muscularis, Gr. IV	Numerous foci of urothelial hyperplasia some with hyperchromatism and early intraurothelial cancer (fig. 25)
W. V.	[illegible]	M	[illegible]	Recurrent hematuria, 3 years. 3 previous fulgurations	Total cystectomy: Bladder measured 12.2 cm. in diameter. Tumor occupied base and left wall above and around ureteral orifice. It was roughly circular & raised 0.2 cm. above mucosa	Preponderantly anaplastic infiltrating carcinoma of urinary bladder with involvement of muscularis, lymphatics and vessels; Gr. III-IV	Foci of urothelial hyperplasia, "tongue" formation intra-urothelial carcinoma (figs. 18, 19 and 20).
P. M.	R118	M	[illegible]	Recurrent hematuria, 15 years. Fulgurations, 13 years. Suprapubic, radium, 12 years ago. Radiotherapy, 1 yr. ago. Transurethral resection, 3 months ago	Total cystectomy: Bladder measured 5.0 x 6.0 x 6.0 cm. Large fungating ulcerated tumor on anterior surface 1.2 x 2.0 cm. Rough area on trigone 2.0 x 1.0 cm.	Fairly well-differentiated, partially metaplastic (squamous cell) carcinoma of urinary bladder with invasion of muscularis and lymphatics	Foci of urothelial hyperplasia, squamous cell metaplasia (figs. 21 and 22), "explosive" infiltration (fig. 23), hyperchromatism (fig. 24)

B. Tumor-free bladders
(autopsy cases)

CASE NO. & NAME	PATH. NO.	SEX	AGE	FINDINGS AT AUTOPSY	FINDINGS ON BLOCK SECTION STUDY
1) R. K.	R120	M	60	Glioblastoma	No significant change in urothelium. Occasional cell nest
2) W. C.	R121	M	51	Glioblastoma	As above
3) V. T.	R122	F	31	Rheumatic heart	Cystitis cystica. Chronic cystitis
4) R. S.	R123	M	31	Retroperitoneal tumor	Rare focus of urothelial hyperplasia
5) H. S.	R124	F	68	Hypertension and uremia	Occasional cell nest

CONCLUSIONS

This is a preliminary report. The series is too small and may be a unique one because it consists mainly of cases that had considerable pre-total cystectomy manipulations and operations.

We found in the *grossly normal-looking mucosa* of tumor-bearing bladders varying numbers of *microscopic foci* of cellular activity, some which were definitely malignant and others, which in course of time, would probably have blossomed into grossly obvious growths. The tumor-free bladders showed only occasional foci of cellular hyperplasia.

The findings suggest that in any operation upon the bladder for the removal of a grossly obvious growth, there may already be present in that bladder, *unseen with the naked eye*, areas of hyperplasia and/or beginning anaplasia which in time could result in gross new tumor formation or formations. Many "recurrences" therefore are really the coming of age, symptomatically, of a neoplastic process which may have been initiated before or after operation.

The study suggests that careful inspection of the entire mucosa—where possible with magnifying lens or glass—be made during open operation for bladder tumor. Routine removal of an adjacent cuff of tissue may not suffice. Barely visible foci of cellular activity may be present beyond the cuff. It might be possible to ablate these with some destructive agent.

We found that those bladders which contained papillary tumors, single or multiple, showed a greater incidence of microscopic foci of urothelial activity than did the solid solitary tumors. This conforms with the clinical observation that many of the papillary tumors may first spread in an horizontal plane while the indurated and ulcerative types penetrate earlier in a vertical plane into the muscularis.[18] It has also been observed that papillary tumors are often multiple when initially seen.[19]

The factor of "recurrence" due to regrowth because of incomplete removal could not be evaluated. It was probably not a prominent one.

The factor of seeding or implanting may be an important one. During operative manipulations of a tumor-containing bladder innumerable cells may break off. If cancer cells can grow on artificial media then they ought to grow in tissues of their host particularly in areas of injury. Measures to avoid seeding at the completion of the removal of a bladder tumor should be instituted. Agents that destroy surface or free cells, may help (?podophyllin, ?phenol, ?surface x-radiation). Instruments and gloves should be changed in open operation following closure of the bladder.

The factor of the continued action of a carcinogenic agent is probably the most important one. Operative procedures attempt to remove *the effect*, not *the cause*.

The study was not concerned with the merits of total cystectomy.

The author thanks Dr. G. Cahill, director of the Squier Urological Clinic, Dr. H. Smith, Professor of Pathology, College of P & S, Columbia University, and Dr Edith Sproul, of the Delafield Institute for their kind co-operation in the use of material.

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DISCUSSION

Dr. Edwin F. Hirsch (Chicago, Ill.): Dr. Melicow's problem of determining the nature of the regrowth of tissues following a resection of a carcinoma of the urinary bladder confronts surgeons in other specialized fields of practice. These recurrences in the bladder resemble conditions observed in carcinomas of the larynx. The surface epithelium for some distance about some of these tumors is atypical and unless removed could initiate a recurrence. Surface epithelium undergoes certain morphological changes which are recognized as "atypical" although there is no actual invasion of the stroma. To recognize such microscopic changes by gross examination is impossible. It seems to me that surgeons should consider that cancerous changes occur in tissues beyond the actual gross limits of the tumor and that they must excise widely in the hope that all of the cancerous tissues are removed.

There are many examples of implantation by tumors from the upper levels of the urinary tract, such as the papillary tumors of the renal pelvis with multiple implantations into the ureter. When the primary tumor is removed you try to destroy or remove the others. As regards implantation at the time of the operation, analogous examples of such implantations of the pelvic peritoneum are with carcinoma of the stomach. During an operation, some tumor tissues may be transplanted into living tissues, find the growth conditions suitable and produce an implant.

Another possible element to consider is the stimulus of a carcinogen. Some agent is excreted in the urinary tract which stimulates tissue growth even after removal of a carcinoma. This is something about which in humans, we know little.

Dr. Melicow: I only want to add this: The study does not attempt to answer the question of carcinogenesis. It emphasizes that there may be areas in tumor containing bladders which are undergoing a change but which change cannot be seen at the time of operation. In time these areas can become grossly and obviously neoplastic. We should look upon and handle neoplastic cells as we do pus. Many of the desquamated cells are alive and may "seed" when dropped off, and there is a great chance for them to drop off, particularly during operation, because most malignant cells have less adhesiveness to one another—about 20 per cent less in some types than normal cells. Once seeded, tumor cells should grow readily because what more ideal medium is there for a cancer cell than that of its own host?

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RADIUM THERAPY OF BLADDER CANCER, RETROSPECT AND PROSPECT

B. S. BARRINGER

Radiation therapy of bladder cancer, as generally used today, began in the year 1915, in the old Memorial Hospital. The first cure, Mrs. C. A. G., aged 69, came to the hospital on December 1, 1915. She had a large, somewhat necrotic growth covering the left ureteral orifice. Dr. Ewing pronounced it alveolar cancer, much inflamed, with dilated blood vessels. On January 14, 1916, 100 millicuries of screened radium were placed in her bladder as nearly as possible over the tumor area and left in place eight hours. On February 4, 1916, a cystoscopic examination with Dr. Keyes showed no tumor, and the previously obscured ureter was in plain sight, surrounded by normal mucous membrane. She was cystoscoped last on January 24, 1918. Her bladder was normal. In October 1926, she died suddenly of a heart attack. There had never been any return of her bladder tumor.

This one case encouraged us to believe that radium had unusual and unexplored possibilities in the control of bladder cancers. For the next 25 or more years we devoted ourselves at the Memorial Hospital to this task. The task naturally started with the problem of accurate application of radium to bladder tumors and to the determination of what kind of bladder tumors were permanently cured by radium.

Surface application of screened radium was used until early in 1920. Duane, the physicist at the Memorial, developed the glass seeds of radium and I had made by our mechanic the first cystoscopic needle for implanting these glass seeds into a tumor.

Shortly thereafter, Fialla developed the gold seeds of radon which screened out the irritating beta rays, the chief disadvantage of glass seeds. Since then there has been no change in the radon seeds. These gold seeds were implanted with the same cystoscopic needle.

We then sought to widen the field of the implantation of radon seeds by opening the bladder, cauterizing off any projecting portions of tumor and implanting the seeds directly into the tumor base. We reserved the cystoscopic implantation for smaller tumors of the bladder base and lower lateral walls. We placed no restrictions on the size or extent or induration of the tumors which we tried to control by the suprapubic implantation of radon.

After trial and error we finally determined on seeds of a strength of 2 millicuries as most suitable for our work. In the suprapubic approach these seeds were implanted, one to each square centimeter of tumor base, the seeds extending to the edge of the base. The entire implantation was done at one time.

The cystoscopic implantation was quite different; a fractional one. Only 10 or 12 seeds were used at one time. The patient was re-cystoscoped in a month and if the tumor destruction was incomplete more seeds were implanted. Small

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 16, 1951.

tumors, papillary or infiltrating could be completely implanted at one sitting. If the tumor was larger and we believed it could be destroyed cystoscopically, as many as four or five implantations were done, about a month apart. If the tumor became entirely sloughy with no viable red areas, we considered the tumor destroyed and simply watched it cystoscopically.

By this method most failures were due to not using enough seeds or by attempting to control too large a tumor. Considerable experience was necessary to determine which tumors could be cured cystoscopically, experience and a good deal of intelligent persistence. From a quarter to a third of all tumors that came to us we tried to control in this way. From one of our reports we employed the suprapubic method in 129 cases and the cystoscopic in 44.

FIVE YEAR CONTROLS

In the last report in the *Journal of the American Medical Association* ("Twenty-five years of Radon Treatment of Cancers of the Bladder") we recorded "of 94 cases of papillary cancer, including 7 cases of atypical papilloma 49 or 52 per cent were 5 year cures. Of 127 cases of infiltrating cancer there were 30 or 23.6 per cent 5 year cures." If the two types were combined there were 35.7 per cent 5 year cures. No pure papillomas were included in this series.

There is no question that many of the 127 cases of infiltrating carcinoma were totally beyond control by radium. Someone, however, had to do experimental work on these tumors and we did it. Our statistics suffered. We learned however, that the solid infiltrating fixed tumor occupying a third or a half of the bladder very rarely could be cured by radium.

These are the tumors that the present day "total cystectomists" are aiming at and with them rests the burden of proof of the value of total cystectomy.

FUTURE PROSPECT OF RADIUM TREATMENT

At the time when the new Memorial Hospital emerged from the old, both at the Memorial and in the country at large, enthusiasm for the radon treatment of bladder cancers began to wane. This was due in noncancer hospitals to the difficulty in obtaining radon seeds in proper amounts. In these hospitals urologists always had operative instruments at hand, but no radium. Radon treatment was obviously from the very start a method to be used in special cancer hospitals where radon seeds were at hand in any strength and amount. Another reason for this trend away from radium was the perfection of the operation of total cystectomy. There was a glamour in doing this operation which the humdrum implantation of radon did not offer. I think it only fair in comparing these two methods of treatment, radium and total cystectomy, to emphasize the relative [illegible] of radium implantation either cystoscopically or suprapubically as contrasted with the severe and extensive operation of cystectomy with its possible [illegible] of ureter orifice stricture and hydronephrosis.

A number of competent urologists who have been developing and advocating [illegible] of total cystectomy have severely criticized radium results. With [illegible] has one of these from personal experience sought to learn the possibilities of radium. No one, however, in comparing the two methods, can afford to pass over lightly the record of five year controls of bladder cancer quoted in this paper.

In the future, I believe that urologists should swing back to perfecting themselves in the cystoscopic method of applying radium, in fractional doses as outlined above. They can do this wherever they prefer to work simply ordering 10 to 12 seeds of 2 millicuries each for each cystoscopic implantation. They do not have to have unlimited supplies of seeds at hand to draw upon, as is necessary when the suprapubic implantation is indicated for a tumor of perhaps indeterminate size.

If they believe the cystoscopic control is impossible and decide on a purely surgical approach to the problem, let them consider the almost neglected method of Beer and Verne Hunt of wide removal of the tumor where possible and reserve total cystectomy for cases with many small cancers scattered widely over the bladder or in large infiltrating cancers. Both of these in our hands have proved beyond control by radium.

New Canaan, Conn.

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CONGENITAL MULTILOCULAR BLADDER: A CASE REPORT

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Congenital bladder divisions occur so frequently in clinical urology that many men have considered such anomalies of only academic interest. The multiplicity of classifications and the variations in terminology of congenital bladder divisions have resulted from this limited attention. Through the presentation of a case report of a congenital multilocular bladder, it is the purpose of this paper to define the terminology and proffer a simplified classification.

Bladder division has been selected as the general term because its extension includes reduplication of the bladder, septal divisions, contraction rings and cystic loculations of the bladder. Diverticula, which are by definition outpocketings rather than partitions, are excluded. The proposed classification is outlined as follows:

Congenital Bladder Divisions

1) Sagittal or Longitudinal Divisions
    A) Complete reduplication of the bladder (fig. 1, *A*)
    B) Incomplete reduplication of the bladder (fig. 1, *B*) (vesico-bipartite)
    C) Complete sagittal septum (fig. 1, *C*) (vesico-duplex)
    D) Incomplete sagittal septum
2) Frontal or Transverse Divisions (fig. 2)
    A) Complete frontal septum
    B) Incomplete frontal septum
    C) Hour-glass bladder
3) Multilocular Bladders (fig. 3)

Diverticula can be differentiated from bladder divisions by the usual criteria. A diverticulum usually does not have a muscular coat, or the muscle has been thinned out; although the septum in a division may not have a muscular coat, some part of the wall of the division is continuous and identical with that of the bladder. A diverticulum invariably has an opening into the bladder which is usually small. In divisions the communications may be of any size or entirely absent. A diverticulum rarely has a ureter opening into it whereas in divisions, each lobule usually has at least one ureter except in the hour-glass type. Finally, diverticula are most frequently secondary to obstruction; and other changes are found, such as trabeculation, cellules and hypertrophied musculature.

Sagittal or longitudinal divisions of the bladder form two bladders or partitions of one bladder by a cleavage plane or septum which divides the organ into right and left sections. Many embryologic explanations have been offered for this phenomenon, but the evidence seems to indicate that they represent various degrees of splitting of the bladder anlage; complete separation results in two bladders or reduplication. Sagittal septa and incomplete sagittal septa are

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[illegible] Meeting, American Association of Genito-Urinary Surgeons, Skytop, produced depending on the extent of separation. In all ten cases of complete reduplication cited by Burns, there was reduplication of other cloacal organs.

A reduplicated bladder is defined as two distinct and separate bladders, each having a urethral orifice. In incomplete reduplication, there are two compartments separated by an indentation in the external contour of the bladder and not merely a septal separation.

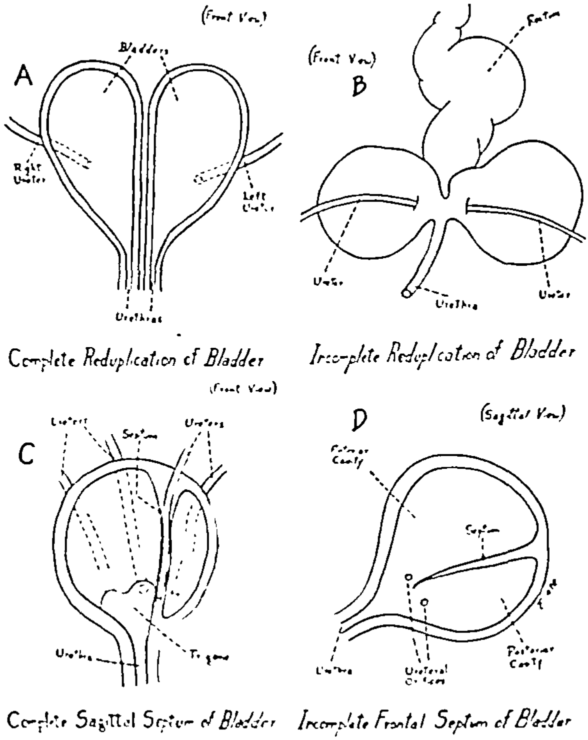

FIG. 1. *A*, complete reduplication of bladder showing two bladders, each with one urethral orifice. *B*, in incomplete reduplication of bladder, one urethra drains both compartments whose separation is evident in external configuration of bladder. *C*, sagittal septum divides bladder into right and left portions without indentations in external configuration. Incomplete sagittal septum does not extend full longitudinal diameter of bladder. *D*, frontal septum divides bladder into anterior and posterior compartments. In hourglass bladders, septum is short and contraction ring extends around entire transverse circumference.

A complete sagittal septum walls the bladder into two chambers without change in the external configuration. An incomplete septum is one in which the septum has an opening.

Frontal or transverse divisions of the bladder occur less frequently. There are two favored embryologic explanations: The first is that there is an excessive constriction between the urogenital and vesico-urethral portions of the ventral cloaca, which results in a frontal septum, or sometimes, into an hour-glass contraction. The second explanation postulates a supernumerary cloacal septum which indents the epithelial wall of the bladder and carries with it an evagination of peritoneum. Hour-glass bladders are included in this group. In Caulk's 2 cases and Young's 5 cases of congenital hour-glass bladder, the transverse bands or septums were found only in the posterior portions of their bladders. The hour-glass appearance seems to be due to spastic contracture of the musculature in the same circumference as the anatomical transverse septum.

We have found only 1 case in the literature of complete frontal septums, that of Schwartz, in a female. The anterior bladder was drained by the normal urethra, the posterior by a meatus below the first. The patient had incontinence from the posterior bladder which had a capacity of 80 cc. Young wonders if this was not a case of cystic dilatation of the lower end of a supernumerary ureter with an opening into the vestibule.

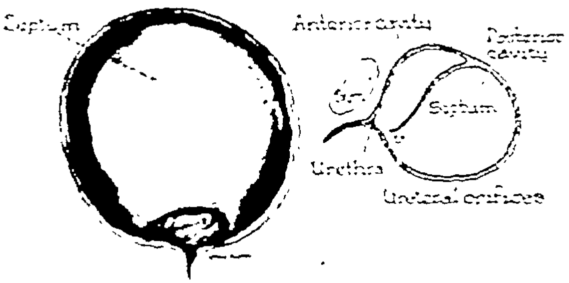

Fig. 2. Sagittal view of frontal septum and appearance of septum through cystotomy incision.

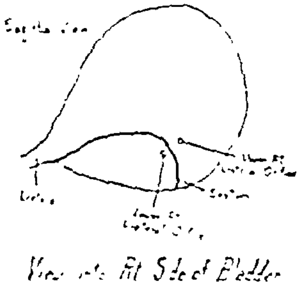

Fig. 3. Multilocular bladders have bladder within bladder. Loculus extends out from the [illegible] and may not communicate with bladder cavity.

Congenital multilocular bladders of ureteral origin make up the last division. Their occurrence is more frequent and necessarily of clinical interest because of an associated ureteral obstruction. The loculus always contains a ureter, the posterior portion is normal bladder wall. The intravesical septal portion is lined on both sides with mucous membrane but the intervening tissue is fibrous. Regarding their formation Edward's description follows:

> On other occasions it appears that the ureter has failed to perforate the [illegible] and submucosa of the bladder wall although the remainder of the tube [illegible] it passes through the muscularis. The absence of muscle fibers in the [illegible] septum is in favor of this interpretation, as the bladder musculature [illegible] at a later stage of development than the union of bladder and

ureter. In such a case the second loculus is really a cystic dilatation of the lower end of the ureter occurring in the bladder cavity. The cyst may subsequently perforate in which case there is a communication between the two cavities but failing such a perforation the cyst remains isolated from the body surface."

Chwalla's findings support the above descriptive explanation. In embryos between 20 to 28 mm. he found that the ureters are closed off from the bladder proper by membranes. If these persist the secretions of urine balloon the membranes to form secondary chambers, within the bladder but with no communication to the lumen of the bladder. Thus, a loculus is formed due to failure of perforation of this membrane. Brown reports that in mice whose metanephros secretes on the fifteenth or sixteenth day, a hydro-ureter and hydronephrosis are found for 4 to 5 days later until some lower ureteral obstruction is relieved.

Multilocular bladders have not been subdivided but there can be as many loculations as there are ureters. In so far as these locules appear to be of ureteral origin they usually are found in the base of the bladder. The ureter almost always shows evidence of back pressure.

CASE REPORT

A 16 year old white girl was admitted to the Long Island College Hospital on June 27, 1950 with complaints of intermittent, colicky, abdominal pains in both lower quadrants for years. Associated with the pains were bouts of fever, pyuria and dysuria.

Physical examination showed a pale, thin, undernourished girl with pain but no tenderness in the lower abdomen.

Laboratory reports: Red blood cells 3.90, hemoglobin 11 gm., white blood cells 7,350, urea nitrogen 17.8 mg. per cent, creatinine 1.8 mg. per cent, chlorides 590 mg. per cent, CO_2 content 61.6 volumes per cent. Urea clearance 6.1 per cent average normal function. Phenolsulfonphthalein excretion 5 per cent in 2 hours. Urine showed a specific gravity of 1.005; 3 plus albumin and many red blood cells and white blood cells.

Cystoscopy on June 28, 1950 showed a large dilated bladder. Dilated right and left ureteral orifices were seen. Extending from the interureteric ridge around the sides of the bladder to the internal urethral orifice was a septum in which a small perforation was seen. Retrograde pyelograms demonstrated bilateral hydro-ureter and hydronephroseis. Cystograms gave the added information that there was complete reduplication of the right kidney and ureter demonstrated by reflux of sodium iodine up the ureters (fig. 4).

From the foregoing findings it was deduced that this was a bilocular bladder and complete reduplication of the right kidney. The ureter from the lower pole of the right kidney and the left ureter emptied into the bladder, above the septum. The orifice of the ureter from the upper right kidney was below the septum.

On July 5, 1950 a cystostomy was done. The septum was found as described. It was circular, biconcave with a ¾ inch margin attached around the base of the bladder. There was a small perforation in the septum. The septum was completely excised forming one bladder cavity (fig. 5). Below the septum the other right ureteral orifice was found to be greatly dilated. The bladder neck was found to be adequate. A Pezzer tube was inserted.

The patient's course was uneventful. She was sent home on the thirteenth postoperative day with the Pezzer tube in situ. After 2 months of suprapubic

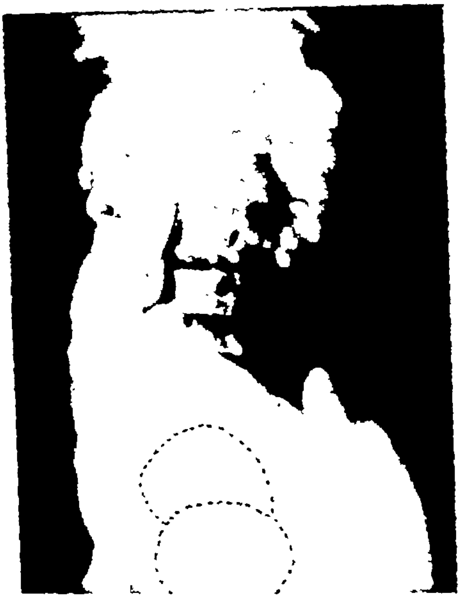

FIG. 4. Oblique cystogram of patient demonstrating bilateral ureteral reflux of iodide, reduplicated right kidney and marked hydro-ureter and hydronephrosis. Bladder and [illegible] have been marked in.

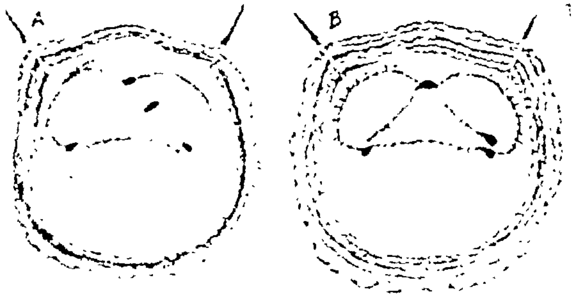

FIG. 5. A, View into bladder at time of operation shows septum extending from inter-[illegible] lateral walls of bladder to point below urethra. Two dilated ureteral [illegible]. Ragged perforation in septum probably was made at time of cystoscopy. [illegible] has been excised and lumen of bladder is continuous. Second right ureteral [illegible] below septum is now visible. Attachment of septum was so broad [illegible] to secure hemostasis.

[illegible] the tube was removed and the cystostomy wound was healed. The [illegible] gained 20 pounds in weight, is active in school and is much better. [illegible] persistent ureteral reflux but the hydro-ureters have [illegible]. Her urine shows a few pus cells. On January 12, 1951 [illegible] 15 [illegible] clearance was 20.7 per cent average normal function. The pathologist reported that the septum consisted of connective tissue lined on both sides by squamous and transitional epithelium. No smooth muscle was found in the septum.

DISCUSSION

Wehrbein, Michelson, Edwards, Mezan and Boulgakow and Malek have reported cases of multilocular bladder. There are undoubtedly many others which have been classified as sagittal or frontal septal bladders or even as ureteroceles. *Our inclination is to regard ureteroceles as having the same embryologic* formation as loculated bladders. In both conditions the ureteral membrane rails to rupture completely. If there is a small perforation the membrane balloons out into a ureterocele. If there is no opening, a loculation is formed in the bladder which may, however, rupture at a later date when the septum has fully formed.

Congenital bladder divisions have been classified into three main categories: sagittal, frontal, and loculated bladders.

Although the last group could be fitted into the first two divisions on the basis of the gross anatomical appearance of the septum, it is our conviction that multilocular bladders deserve a special consideration. Embryologically their formation is different and moreover, they have special clinical significance. In all multilocular bladders there is obstruction to one ureter. The secretion of urine into this closed loculus can form a bladder within the bladder which often interferes with the other ureter or ureters. A report has been given of a multilocular bladder with advanced urologic damage which achieved a good result upon recognition and excision of the septum.

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INCOMPLETE FRONTAL SEPTUM OF BLADDER COMPLICATED BY CONGENITAL URETHRAL VALVES AND COMPLETE REDUPLICATION OF UPPER LEFT URINARY TRACT

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A complete article on the subject of reduplication of the bladder has been published by Burns, Cummins and Hyman (1947). This article reviews the literature to that time, adds an additional case, and sets forth a classification of the subject as follows:

1) Complete reduplication of the bladder
2) Incomplete reduplication of the bladder
3) Complete sagittal septum of the bladder
4) Incomplete sagittal septum of the bladder
5) Complete frontal septum of the bladder
6) Incomplete frontal septum of the bladder

By special permission of the authors, we are reprinting the illustrations used by them in their original article (fig. 1). This is being done for two reasons: first, a graphic review; and second to illustrate more accurately the subdivision of the classification into which the case we are reporting correctly fits, namely, No. VI.

The general subject has been very thoroughly and exhaustively presented by Burns, Cummins and Hyman. It is not our purpose to modify or attempt to enlarge or to improve upon their accepted classification. We simply desire to add another case to the series already reported.

CASE REPORT

A boy aged 7 was referred to the Department of Urology, August 3, 1947, with a chief complaint "inability to hold his urine (stress incontinence) and persistent pyuria." His father, mother, and one brother were living and well. The father at the age of six had enuresis. One maternal aunt and a maternal uncle also had enuresis in childhood, which complaint had continued into adult life. The familial history of enuresis caused the parents to accept the child's condition as [illegible] and they were resigned to it. Medical consultation was, thereby, delayed. The personal history included mumps, chicken pox, and measles. He gave no history of other serious illnesses, surgery, or accidents. Each winter the patient had had a cold or an attack of "streptococcic throat." At the age of 5, he had a particularly severe throat infection requiring "sulfa drugs." The mother stated that the patient had always been a "bed-wetter" and that since starting school, he had [illegible]. Urine analyses had shown intermittent pyuria.

For a period of 2 months in 1946, the patient was treated for "cystitis." At this time [illegible] in the urine, in addition to the pyuria. Periodic attacks [illegible] "doubled up" the patient. These pains were relieved by urina-

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[illegible] North Central Section, American Urological Association, [illegible] tion. The mother could remember a number of such episodes. She further stated that the child would tire quickly, especially while playing, and would come into the house to lie down.

Physical examination, except for the genito-urinary system, presented no abnormal findings. The external genitalia were normally developed. The bladder was palpable suprapubically and extended midway between the pubic bone and the umbilicus. No other masses were present. The superficial veins of the thorax appeared dilated. The blood pressure was 110/60. No audible murmurs were present except a split pulmonary second sound.

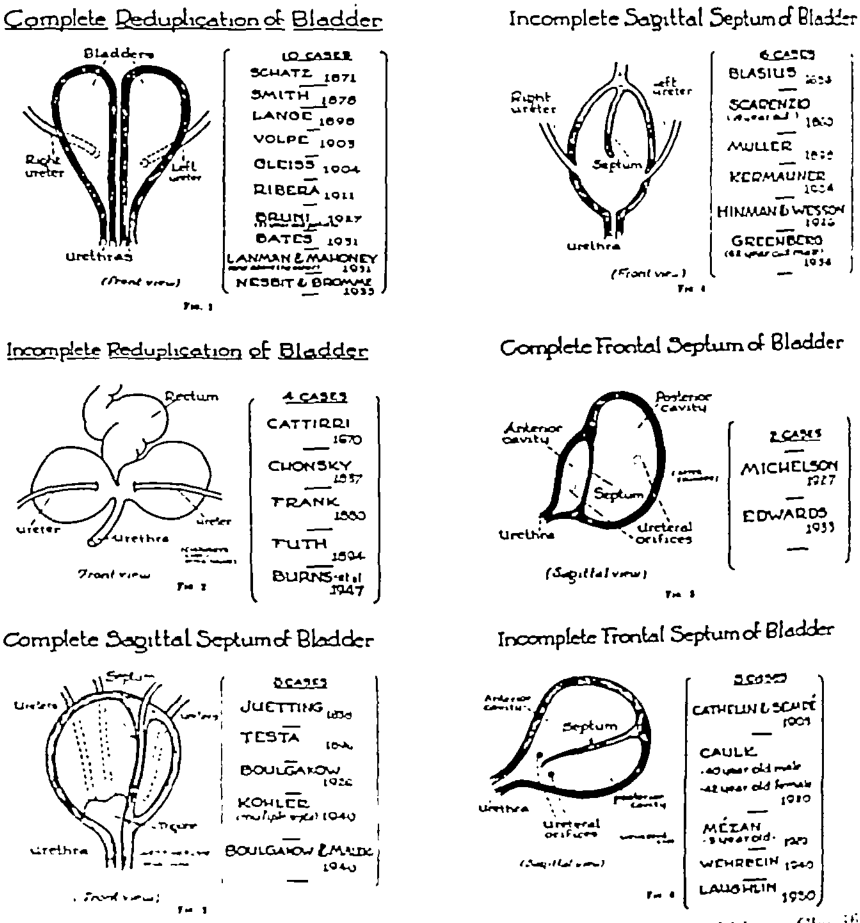


FIG. 1. Incomplete reduplication of bladder with congenital solitary kidney. Classification set forth by Burns, Cummins and Hyman. J. Urol 57: 257, 1947.

The blood count was within normal limits. All specimens of urine showed a large number of white blood cells and on occasions, numerous red blood cells, accompanied by the usual positive albumin reaction. No albumin was present in other specimens. Urine cultures repeatedly showed nonhemolytic streptococcus. The Kline and Wassermann tests were negative. Repeated blood chemistry tests showed an absence of azotemia

The anterior urethra admitted an infant cystoscope with ease. Bladder capacity was enormous (1,000 cubic centimeters). The anterior urethra was normal. The posterior urethra showed two congenital valves arising from the proximal portion of the verumontanum extending tortuously along the lateral walls of the posterior urethra to its roof. These we classified as type two, after Young's classification (fig. 2). Inspection of the bladder revealed the presence of an incomplete frontal septum (after the classification of Burns, et al.). This septum, situated above the interureteric ridge, divided the bladder cavity into an

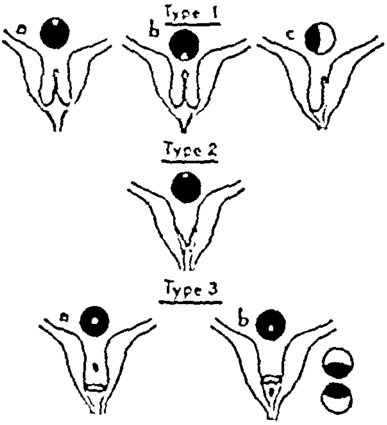
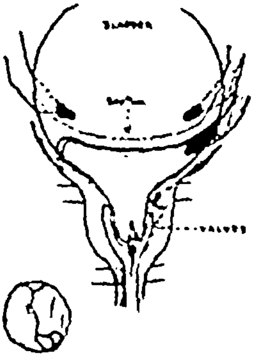
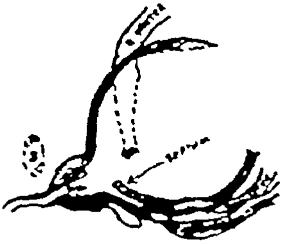


FIG. 2





A No. 4 catheter persistently coiled in the lower portions of the ureters and attempts to perform pyelograms were unsatisfactory at this sitting.

Roentgenological examination under date of August 9, 1947 revealed the catheters coiled in the lower ureters. After injection of the dye, indistinct outlines of the markedly dilated ureters could be faintly visualized (fig. 4).

A *second cystoscopy* was performed August 14, 1947 for the purpose of more thorough study and to obtain better pyelograms. The obstructive influence of the congenital valve formation in the posterior urethra was again apparent. The sphincter was distorted in all directions and the proximal ends of the valve leaflets extended well into the sphincter area.

The two ureteral orifices on the left side were wide open. No instrument could be used which would block them effectively for the purpose of pyelo-ureterograms. The bladder was filled to capacity with 2 per cent sodium iodide and excellent pyelo-ureterograms for this side were obtained by ureteropelvic reflux. A congenital fused left kidney and complete reduplication of the ureter was thereby demonstrated (fig. 5, *A*). A minimal quantity of dye was seen in the right ureter but more accurate information concerning the right upper urinary tract was obtained later by excretory urogram. The bladder was quite large, the upper portion of the bladder extending well out of the lesser pelvis as seen in both the anteroposterior and lateral views (fig. 5, *B*).

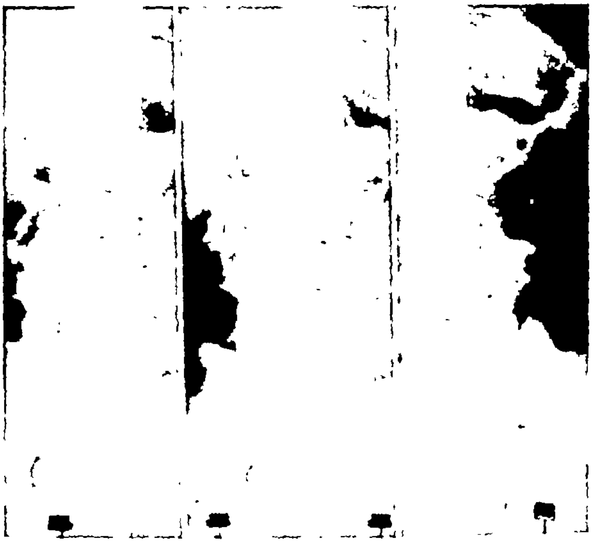


Fig. 4

Excretory urograms revealed fairly good concentration of the dye in the right kidney region, marked dilatation of the right kidney calyces and pelvis with extreme dilatation of the right ureter (fig. 5, *C*). Only faint visualization of the dye is seen in the left kidney region sufficient, however, to disclose marked dilatation of the calyces. Because of the extremely poor function in the left kidney, insufficient dye was present to visualize the left kidney pelvis and ureters. No nephroptosis was present in the upright films and no calculi were present.

Transurethral electrofulguration of the valve leaflets was begun at this cystoscopy. There was no prostatic enlargement. We have seen it in children as a source of vesical neck obstruction. Very little electrofulguration was done on this occasion. Several sittings were planned for their destruction. A postoperative urethral catheter was left in situ.

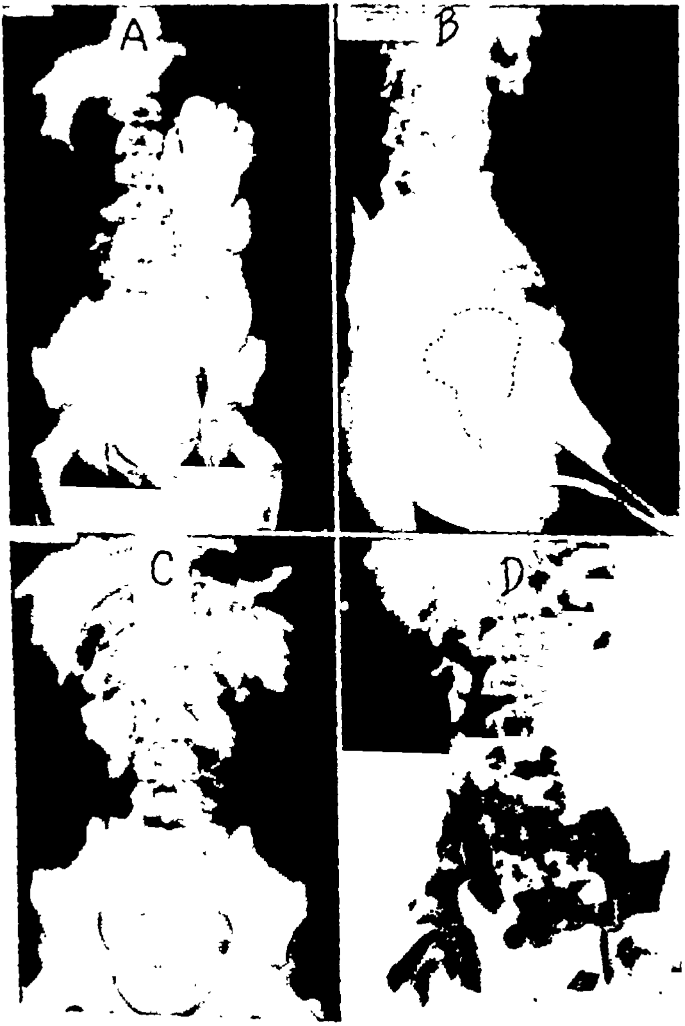


FIG. [illegible]

cystoscopy was performed both suprapubically and transurethrally. There was a marked diminution in the amount of tissue obstructing the posterior urethra and vesical sphincter area, a result of the first electrofulguration. The suprapubic cystoscopy provided a very excellent view of the vesical sphincter area and no major obstruction in this region remained.

The third hospital admission was on November 8, 1947. The patient appeared much improved generally. Excretory urograms showed a good visualization of the right kidney calyces, pelvis, and ureters. There was considerably less dilatation of the calyces and pelvis on this side (fig. 5, *D*). The right renal function was now considered good. The lower third of the right ureter remained dilated, being 2 cm. in diameter of its widest point. The ureters were considered congenitally dilated.

Again, only traces of dye appeared in some of the left kidney calyces even after 30 minutes. The right urinary tract was seen to be gradually diminishing in size and the kidney pelvis was approximately normal size.

A No. 18 McCarthy panendoscope could now be used. This instrument provided better vision and greater operative ease. On this occasion, the incomplete frontal septum was divided with transurethral scissors and the severed margins were fulgurated. This created one bladder cavity. Remnants of the congenital urethral valves were also fulgurated, completing the repair of the posterior urethra. The suprapubic drainage still in process was very assuring and continued to serve us well.

The fourth hospital admission was on December 3, 1947. It was necessary occasionally to replace the suprapubic catheter. This was one of these occasions, this time because of concretions.

Cystoscopy revealed a completely healed and normally patent posterior urethra. There was no vesical neck obstruction. The bladder presented a single cavity. The right ureteric orifice was practically normal in appearance but was situated abnormally high on the right lateral wall of the bladder, considerably above the normal anatomical position. The two left ureters presented no change. Several remnants of the former septum were fulgurated.

The fifth hospital admission was on January 5, 1948. The patient was now 8 years old and in good health. These were all short hospital admissions.

Each cystoscopy provided therapeutic dilation for the posterior urethra and under the most favorable circumstances. A No. 18 McCarthy panendoscope passed freely. The interior of the bladder looked very good indeed. There remained a few remnants of the former septum to be destroyed by fulguration. Thus, the entire false floor of the bladder was eliminated. A suprapubic cystoscopy was again performed. Nothing additional was noted.

Bilateral catheterization disclosed that the persistent pyuria had its origin in both halves of the reduplicated left kidney. A left *nephro-ureterectomy* was decided upon for spring vacation as the patient was in school at this time. The cystostomy catheter could have been removed at this time but it was not.

The sixth hospital admission was on April 11, 1948. Medical consultation disclosed that the patient was ready for operation. The case findings were carefully

ummarized as follows: 1) Obstructive congenital urethral valves had been en-
irely eliminated. 2) The urethra was adequately dilated and patent throughout
s *entire length*. 3) *An incomplete frontal bladder septum* had been destroyed.
) Normal function had returned to the right kidney. 5) A functionless left kidney
as the source of a persistent pyuria. 6) The patient had returned to excellent
ealth. 7) Laboratory findings were normal. There was no azotemia.

A complete nephro-ureterectomy was performed. The patient made a rapid
nd uneventful recovery. The pyuria immediately ceased. During the convales-
ence from this operation, the suprapubic catheter was removed and the cystos-
omy wound allowed to close. It did so promptly.

that the case could have been rushed through more rapidly. In the best interests of the patient, we do not think so.

SUMMARY

The sixth case in the literature of incomplete frontal septum of the bladder is reported in detail. The patient is a child, 7 years old. The case in complicated by the presence of congenital urethral valves which were obstructive in nature, bilateral obstructive ureterectasis and pyelectasis with pyelonephritis, a congenital fused kidney on the left side with complete reduplication of the ureters and persistent pyuria.

The literature on the subject has been reviewed.

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FRACTURE OF PELVIS AND RUPTURE OF BLADDER COMPLICATED BY PYOGENIC ARTHROSIS

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In a review of the cases of traumatic rupture of the bladder treated at St. Francis Hospital during the past 10 years, 2 cases were found in which a fracture extended through the acetabulum in addition to fractures of the pubis and their rami. In both of these cases pyogenic arthrosis subsequently developed. A review of the literature on pyogenic arthrosis of the hip failed to reveal fractured pelvis with a ruptured bladder as an etiological agent. In a review of the urological literature in the past 10 years, no mention was made of rupture of the bladder complicated by pyogenic arthrosis of the hip.

The orthopedic literature cites only 3 cases of osteitis pubis complicated by a pyogenic arthrosis. The mechanism of dissemination, it is believed, may not be comparable to that experienced in the cases cited here. In osteitis pubis the condition is one of initial periosteal trauma which usually occurs at the time of suprapubic or retropubic prostatic surgery with infected urine seeping over the traumatized area. This may result in an inflammatory process which spreads subperiosteally with extension of the pubic and ischial bones. On three occasions the acetabulum was involved but open hip surgery was not required. Bone segments removed during the active phase of this condition revealed osteomyelitic changes. The mechanism of dissemination of the infection from a ruptured bladder to involve the hip joint may be comparable to that of the extension found in osteitis pubis. Spread by way of the lymphatics or perivascular routes is feasible considering the relationship of the obturator vessels to the perivesical space with the acetabular vessels being a segment of the posterior branch of these vessels. Direct extension to the hip joint through the fracture line in the acetabular wall cannot be excluded in that this occurred in only two cases of ruptured bladder associated with an acetabular wall fracture.

the right pubis and its right superior ramus. At operation the space of Retzius and the perivesical space were found to be filled with bloody fluid. The anterior bladder wall was torn for approximately 6 cm. A jagged fracture of the right pubic bone was found. The bladder was repaired and drained suprapubically as were the perivesical spaces. His postoperative course was satisfactory and he continued to improve. X-rays taken 7 days following admission showed no additional information from the original film.

During his postoperative course, the patient continued to have a low grade afternoon temperature elevation. Urine studies showed 8–10 red blood cells per high powered field and 50–60 white blood cells per high powered field. A culture of the urine on February 7, 1939 was reported as containing gram negative bacilli, gram positive cocci in short chains and gram positive cocci in clusters.

The patient began to complain of pain in the right hip on February 17, 1939, 30 days after admission. An x-ray of the right hip showed narrowing of the articular cartilege space of the right hip (fig. 1,*B*) with destruction of the articular bony cortex on the superior or contacted portion of the femur. The opposing subchondral bony cortex of the acetabulum had likewise disappeared. Orthopedic consultation was requested and one of us (J. J. F.) saw him and found swelling and tenderness anteriorly over the right hip. Passive and active motion was not possible beyond 20 degrees of flexion because of pain. Aspiration of the right hip revealed 25 cc of brownish, purulent material; smears and cultures of this fluid showed gram positive cocci in clusters. The next day, an anterior arthrotomy was performed on the right hip joint. The capsule of the joint was found to be thickened. The cartilage over the noncontacted region was thinned and was completely destroyed over the weight bearing portion. The subchondral bone was exposed and bloody purulent material was found when the hip was rotated. Rubber drains were inserted and the wound closed about them. The patient was returned from surgery in satisfactory condition and traction applied to the right extremity. After the arthrotomy was performed, the patient's elevated temperature returned to normal in 18 days. Extensive drainage from the hip wound continued for approximately 12 days. Culture studies of the

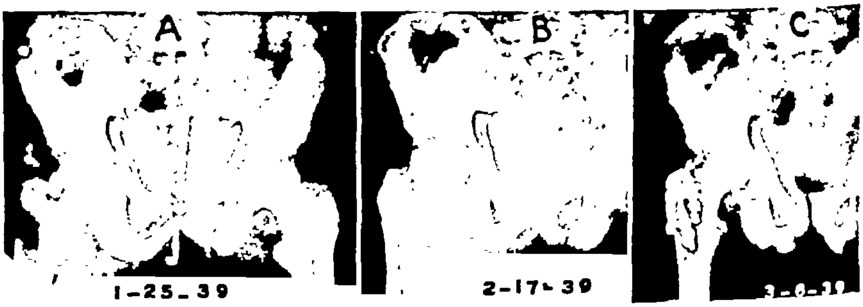

FIG. 1. *A*, x-ray of pelvis showing fractures of pubis, acetabular wall, sacrum and coccyx. *B*, x-ray of pelvis 30 days after admission showing narrowing of articular cartilage space of right hip joint with destruction of the articular bony cortex superiorly. *C*, x-ray 7 weeks after admission showing advanced destructive change of right hip. Sinus where arthrotomy was performed injected with radio-opaque medium.

found in the joint space of the right hip revealed gram positive cocci in clusters.

On March 9, 1939, because of continuing pain in the hip, a body cast was applied. X-rays were made after injection of the draining sinus with radio-opaque material (fig. 1,C), and further destruction of the femoral head and acetabulum was revealed. The tract was found not to extend to the medial acetabular wall or into the pelvis. Two days later he began to complain of frequency. His urine showed an acid reaction, marked pyuria and occasional red blood cell. He was given mandelic acid and urinary acidifiers. His symptoms became progressively worse and were associated with a temperature elevation. Windows were cut in his cast and the hip wound exposed. This failed to reveal active suppuration. It was then believed that he had acute pyelitis. The temperature was 104F. He was given a high vitamin A, acid-ash diet and intravenous fluids with continued improvements. His suprapubic and hip wounds were healing well with minimal drainage. The cast was removed on April 28, 1939, and ambulation begun, with the patient on crutches. X-rays on May 12, 1939 revealed multiple calculi in the right kidney. He left the hospital on May 20, 1939. At subsequent x-ray examination it was found that his multiple right renal calculi were passing into the ureter. He re-entered the hospital on July 22, 1939 because of severe right flank pain. A right ureterolithotomy and right pelviolithotomy were done. On February 1, 1941 a calculus was crushed in the bladder and removed by urethral instrumentation. His last retrograde pyelograms in October 1940, revealed two partly calcified ureteral calculi on the right side at the level of the superior surface of the sacrum. No gross dilatation of the calyces could be demonstrated.

of pains in the right hip which were thought to be due to his pelvic fracture. He continued to drain a sero-sanguinous material through the suprapubic wound. On May 14, 1948 an indwelling urethral catheter was placed in the bladder. His temperature curve then fell to an average high of 99.5F. He continued to complain of intermittent bouts of right hip and low back pain on the right side. On May 14, 1948, the patient experienced pain of increasing severity in the area of the right hip. At this time, motion beyond 50° of flexion caused pain. This restriction was considerably more than the limited motion seen at initial examination because of the pelvic fractures. Aspiration failed to reveal any exudate in the joint.

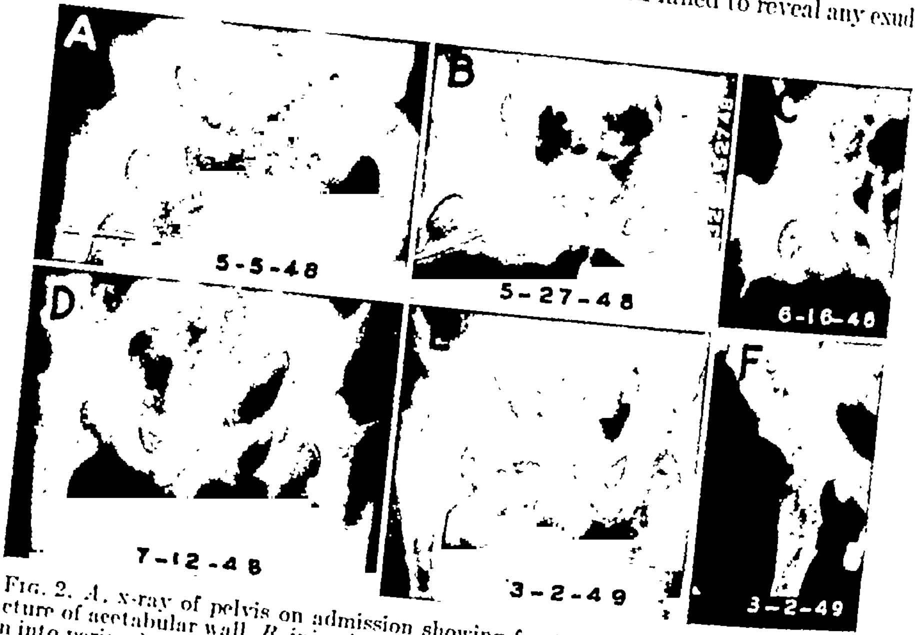

FIG. 2. *A*, x-ray of pelvis on admission showing fracture of pubic bone and rami, and fracture of acetabular wall. *B*, injection of urethra with opaque medium reveals extravasation into perivesical space. *C*, x-ray of pelvis 6 weeks after admission showing narrowing of articular cartilage space of right hip. *D*, x-ray 4 weeks later showing progressing destructive change. *E* and *F*, anterior and lateral view x-rays of right hip made 10 months following surgery showing that some reparative process had occurred.

Injection of the urethra with an opaque medium on May 27, 1948 (fig. 2,*B*) revealed extravasation into the soft tissues immediately below the pubic symphysis in the area in which multiple fractures involved both pubic bones. As noted previously, an indwelling urethral catheter was passed to the bladder on May 14, 1948 and by June 2, 1948, when another x-ray study following injection of an opaque medium was done, no evidence of extravasation was found. Repeated x-rays of the hip did not show any involvement until June 16, 1948 (fig. 2,*C*). At this time narrowing of the articular cartilage space and loss of the articular bony cortex of the femoral head and acetabulum were seen. This was most marked on the weight bearing portion. Considerable absorption at the site of the pelvic fractures with a resulting defect at this site was also seen.

On June 16, 1948, another aspiration was performed after positive x-ray evidone and again no material was obtained. The patient then continued to experience pain in the right hip. No motion was possible at this time. On July 12. 1948 an aspiration of the hip joint was done and 1 cc thin fluid was obtained. A culture yielded hemolytic B. coli. X-ray examination of the right hip on July 12. 1948 *(fig. 2.D) showed increased destruction of the right* hip joint. There was evidence of sclerosis about the right sacroiliac joint.

The hip and right sacroiliac pain persisted and on September 17, 1948 a body cast was applied extending to the knee on the right side. In November 1948, he became ambulatory without the use of crutches. When last seen, on March 5, 1949, the hip was in neutral position and he had 60° of moderately painful motion. Anterior and lateral view roentgenograms (fig. 2.*E* and *F*) showed a reparative process of the hip with no appreciable change in its right sacroiliac joint. He still complained of considerable pain in the sacroiliac area and in back of his hip joint. Anteroposterior and lateral view *x-rays showed a reparative* process as compared to previous x-ray. The advisability of an arthrodesis of the hip was discussed with the patient if his symptoms persisted.

SUMMARY

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TREATMENT OF CARCINOMA OF MALE URETHRA BY RADICAL SURGICAL INFRAPUBIC REMOVAL: CASE REPORT

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Extensive carcinoma of the male urethra, in the absence of discernible metastasis, is amenable to radical urologic surgery. This report is presented to stress the rehabilitation of a seemingly incurable patient through multiple successive operations. The infrapubic approach for radical removal of the entire or subtotal length of the urethra is described. We cannot speak of cure in this case as an adequate time interval has not elapsed. However, there has been no recurrence of carcinoma after 22 months of observation.

CASE REPORT

A. C., No. 225346, a 60 year old restaurant worker, was admitted to the Urologic Section, Radiologic Division, Philadelphia General Hospital on June 24, 1949. His chief complaint was a painless, odoriferous, fungating mass in the scrotal perineal region, associated with difficulty in urination. The acute phase of his illness began 8 months prior to his admission to the Philadelphia General Hospital. A history of urethral stricture covered a span of 25 years, during which time numerous urethral sounds had been passed.

The patient stated that he had had gonorrhea at approximately 22 years of age while working as a ship builder in Africa. He came to the United States at the age of 35 years and shortly thereafter urinary difficulties began. He was treated intermittently with urethral sounds.

In 1939, at 50 years of age, a perineal urethrotomy was performed for an impassable stricture. Following closure of the urethra, sounds were again intermittently passed.

He was admitted to another hospital in Northern Pennsylvania on October 5, 1948, for acute urinary retention accompanied by a fulminating perineal, periurethral abscess. A suprapubic cystostomy was performed, followed by incision and drainage of the abscess. Perineal and scrotal fistulas developed.

On December 4, 1948, under spinal anesthesia, the posterior urethra was dilated through the suprapubic cystostomy opening, and at the same time the anterior urethra was dilated in the usual manner. A catheter was passed to splint the urethral stricture and suprapubic drainage was maintained. On December 16, 1948, the fibrous perineal fistulous tract, which *extended into the* membranous urethra, was removed. Microscopic examination of this tract disclosed inflammatory tissue. On removal of the perineal drain the tract continued to drain purulent material. On April 11, 1949, excision of the fistula was again performed. Histologic study of this second specimen showed inflammatory changes. The patient was discharged on permanent suprapubic catheter drainage.

Read at annual meeting, Mid Atlantic Section American Urological Association, Old Point Comfort, Va., April 11, 1951

On June 1, 1949, the patient was again hospitalized. The perineal fistulas were removed from the same area and external urethrostomy was performed. The cystostomy opening was then allowed to close. Following this, there was rapid proliferation of tissue through the perineal fistula, biopsy of which proved to be squamous cell carcinoma.

He was referred for treatment to the Philadelphia General Hospital on June 21, 1949.

The patient was a well developed man, younger in appearance than his stated age. A pungent, uriniferous odor emanated from his person. The patient was in no acute distress. The temperature, pulse and respiration were normal. Blood pressure: systolic 170, diastolic 80. The head, eyes, ears, nose, throat, and neck revealed no abnormalities. The size, rate and rhythm of the heart were normal. The chest was slightly emphysematous and the lungs were clear. There was slight hyper-resonance to percussion. The abdomen was scaphoid. No masses were palpable. A firm, healed suprapubic scar was present. No hernias or inguinal nodes were palpable. The extremities were normal.

Multiple surgical scars were present on the dorsum and lateral surface of the penis. The scrotal raphe was displaced and depressed by a dense contracted scar, which resulted in a bifid scrotum. In the central perineal area, below the scrotal junction, a urethrostomy opening was surrounded by white granulating, cauliflower-like tissue, approximately 5 cm. in diameter. Urethroscopic examination was not successful. A filiform, when passed through the anterior urethra, emerged near the urethrostomy opening. It was impossible to pass a filiform through the urethrostomy opening into the bladder since the tumor obliterated landmarks. The rectal sphincter tone was poor. The prostate was small, symmetrical, and benign. There appeared to be infiltration into the area of the membranous urethra.

retropubic area was healthy in appearance. The interior of the bladder and posterior urethra were inspected and found free of growth. A section of the posterior urethra and posterior vesical lip was obtained for biopsy which was subsequently reported as chronic cystitis.

The postoperative course was uneventful. The suprapubic tube functioned well and the patient's perineum remained dry. The foul discharge and area of excoriation around the side of the tumor were lessened.

July 26, 1949: Infrapubic radical block removal of the penis, perineal skin with tumor, the entire urethra including the verumontanum, distal half of the prostate and urogenital diaphragm was performed under continuous cyclaine spinal anesthesia.

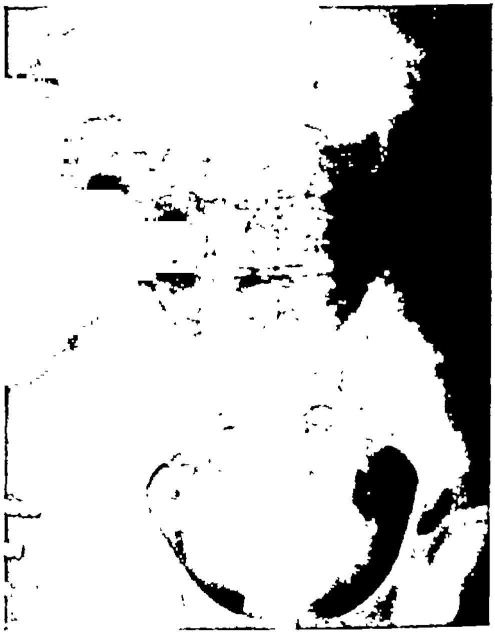
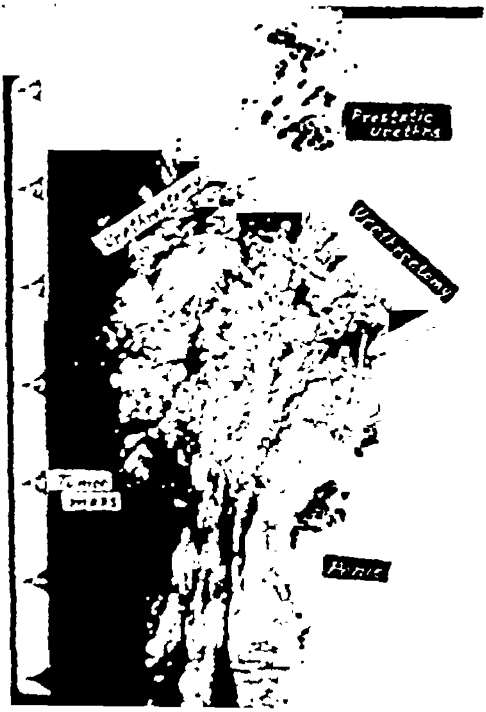


FIG. 1. Normal preoperative excretory urogram, July 6, 1949

A tennis racquet incision was made with the racquet portion about the base of the penis. The handle of the incision was extended inferiorly in the midline of the cleft scrotum, to the healthy periphery of skin above the perineal mass. Scar tissue was excised. The testicles were not disturbed and were retracted laterally. The midline incision above the mass was then extended in elliptical fashion about the perineal metastatic area, leaving a 1 cm. cuff of healthy tissue attached to the lesion. By perineal section the central tendon was severed.

By blunt dissection the penis was freed from its pubic attachments. The dorsal artery and vein were suture ligated. The ischiocavernosus muscles were dissected free and severed from their ischiopubic attachments. The pubic bone and urogenital diaphragm were clearly exposed. The diaphragm was next excised below the pubis, the transversus perinei muscles cut and an infrapubic approach made to the superior aspect of the midportion of the prostate. The tissues in this area appeared healthy and free of malignant involvement. The prostate was divided transversely, the incision severing the urethra just above the verumontanum and extending to the posterior layer of the fascia of Denonvilliers. Sharp dissection next was directed to the lateral and inferior aspects of the perineal mass. The ischiorectal fossae were exposed.

The entire mass of tissue was pulled inferiorly, thus exposing the infrapubic area. By sharp dissection from above downwards, the rectum was freed and the complete mass was delivered with the entire urethra intact and a portion of the



Penrose drains were inserted. Sufficient scrotal tissue was left to cover even a larger defect than the one presented. Superiorly, the scrotal edges were brought together in the midline; inferiorly, the half moon defect remaining in the perineum was easily covered and the edges of skin margin approximated without tension.

The pathologic specimen (fig. 2) consisted of the penis, urethra and inferior portion of the prostate. In the central portion of the specimen, there was an irregular tumor mass which had been bisected. Extending through the tumor mass was the markedly distorted urethrostomy opening. Part of the posterior urethra, prostate and verumontanum could be seen in the upper portion of the specimen. Portions of the urogenital diaphragm and muscle tissue were identified with difficulty due to the proximity of the tumor.

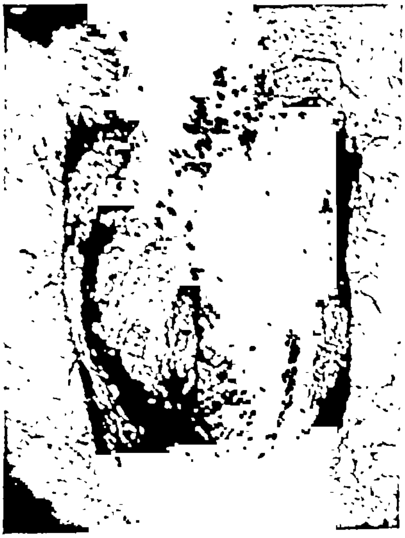


FIG. 3. Scrotum, if uninvolved by malignant process, offers ample amount of tissue for closure of entire infrapubic area. In our case, healing was prompt, and no infrapubic hernia developed following subsequent ureterosigmoidal anastomosis, total cystectomy and prostatectomy.

The tumor mass presented friable, pearly-white cut surfaces. The malignant process extended distally to the level of the penoscrotal junction and proximally up to, but not including, the prostatic urethra.

During the operation the patient received both 5 per cent glucose in water and whole blood. Four hours postoperatively the patient went into incipient shock necessitating the use of whole blood and concentrated plasma. The blood pressure became stabilized within 12 hours.

On the first postoperative day, the patient was maintained on intravenous fluids. The Penrose drains were removed on the second day. On the third day the patient was able to digest a hospital diet and was made ambulatory. Serosanguinous fluid drained for 3 days around the packing. This gradually decreased. The packing was loosened on the eighth day and was removed on the tenth day. Slight drainage of seropurulent material from the opening was treated by irrigation [illegible] sitz baths. The wound completely healed in 3 weeks. At no time did urine drain through the perineum.

Preoperative preparation of the patient for ureterosigmoidal anastomosis was carried out for 7 days.

September 26, 1949: Bilateral ureterosigmoidal anastomosis, total cystectomy and removal of the remainder of the prostate. Continuous spinal procaine was the anesthesia. In preparing the abdomen, the suprapubic catheter was removed.

A long midline incision was made between the symphysis and umbilicus. The scar of the former cystostomy was excised. A sterile mushroom catheter was inserted and a tight closure of the bladder made about it. The bladder was mo-

with medium wire and the skin with Michel clamps. The patient was given 1000 cc of blood during the operation.

The postoperative course was uneventful. Intravenous fluids and whole blood transfusions maintained adequate nutrition and urinary output. On the fourth postoperative day the Levin tube and rectal tube were removed. Blood chemistry studies were within normal limitations. On October 19, 1949, excretory urography disclosed normal bilateral function and concentration (fig. 4). The left renal pelvis was sharply outlined and normal; mild hydronephrosis was noted on the right side. There was slight rectal incontinence of urine but not of fecal material. The patient was discharged on October 28, 1949.

The patient has been seen at periodic intervals and up to the submission of this report has remained in good health.

Rectal incontinence of urine has been a troublesome complication. Improvement in control has been progressive through the use of perineal and anal exercises. Despite this inconvenience, the patient has been able to cope with the problem and presents an appearance of cleanliness.

Blood chemistry studies have remained within normal bounds.

Excretory urography on July 17, 1950 was negative. There was no evidence of hydronephrosis. X-ray of the chest was negative.

The scrotal and perineal regions have revealed no clinical evidence of recurrence of tumor and no perineal hernia.

DISCUSSION

Carcinoma of the male urethra is an uncommon form of malignancy. The case presented is the seventh to have been seen in the Philadelphia General Hospital in 296,244 total admissions from 1936 to 1949. One hundred and ninety-two cases from the literature, including ten of their own, were reported by Lower and Hausfeld in January 1946. Twenty-five cases which were admitted to the Mayo Clinic between 1910 and 1945 were reported by Zaslow and Priestley in 1947. Gailey and Best, in 1949, reported 2 cases in 105,257 admissions from the York Hospital, York, Pennsylvania. McCrea and Furlong reported 230 proven cases in February 1951.

The pathogenesis of urethral neoplasms is speculative. Most urethral carcinomas are squamous cell in type and arise in a canal lined, in most of its extent, by stratified columnar epithelium. Old strictures develop nests of squamous epithelium and possibly this metaplasia is the root from which the carcinoma springs.

An antecedent history of stricture formation is common. Vest stated that 65 per cent of reported cases of carcinoma of the urethra were associated with stricture. Trauma, infection and local irritation appear to be definite contributing factors. The case presented contains a history of these factors which emphasize the importance of the consideration of malignancy in patients with strictures, peri-urethral abscesses and recurring perineal fistulas. A spontaneous abscess in the region of the bulb, without previous urethral disease or instrumentation, must make one suspicious of carcinoma. Visual instrumental diagnosis and [illegible]

The operative steps are unique in this case but should not be accepted as being applicable to every case of carcinoma of the urethra.

Attention is directed to the use of the scrotum as a skin flap in covering the perineal defect.

Rectal incontinence of urine, as it pertains to the operative procedures herein described, is discussed.

Hope should not be abandoned in any of these cases of extensive growth if radical excision can be performed, with immediate safety to the patient's life and ultimate rehabilitation. The authors have presented this case report with this philosophy in mind and with full realization that 18 months with no recurrence of tumor does not mean that the patient is cured.

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the urethra early in embyrologic development by a process of cellular budding with the subsequent development of lumens growing into fully developed compound tubulo-alveolar glands whose ducts empty into the urethra. There seems as little reason for classifying tumors arising in these glands as neoplasms of the urethra as there is for including tumors of the pancreas or biliary system among neoplasms of the intestine. Including tumors arising in the glands of Littre among those of the urethra is understandable because of the small size of these glands, their close proximity to the urethra, and the early involvement of the urethral wall and lumen by tumors originating in them. Three cases have been reported of adenocarcinoma probably arising from the glands of Littre. Olivier and Clunet reported the case of a small adenocarcinoma rising in the urethra of a 52-year-old man. The tumor presented in the form of a small nodule 3 cm. from the urethral meatus and was not considered to have been primary in the urethra but was thought to have arisen in the glands of Littre. Bedrna in 1931 reported a case of an adenocarcinoma probably originating in the glands of Littre in a 57-year-old male whose neoplasm extended from the bulbous urethra to within 3 centimeters of the meatus. This case was included among carcinomas of the urethra by Kreutzmann and Colloff. The only other similar case was reported in 1946 by Cirio whose 80-year-old patient had, in the penile urethra, an adenocarcinoma which was thought to have originated in the glands of Littre. Cirio is the only author who, in reviewing the literature, has attempted to classify tumors of Littre's glands separately from those of the urethra.

There is some evidence to show that glandular tumors can arise in the urethra. Herger and Sauer reported a case of an adenocarcinoma rising in the membranous urethra and gave a brief description of the microscopic appearance with a photomicrograph confirming the diagnosis. Histologically this tumor is very similar to those arising by a process of mucosal metaplasia as will be discussed further. Graves and Guiss in 1941 reported 2 cases of adenocarcinoma of the urethra but no detailed microscopic description was given. Ash, in a discussion of the paper of Graves and Guiss, presented another case of adenocarcinoma of the urethra. Lower and Hausfeld in 1947 reported a case of a papillary adenocarcinoma rising in the urethra of a 40-year-old man. The tumor presented in the form of a hard indurated mass encircling the urethra immediately posterior to the scrotum. The anatomic diagnosis was papillary adenocarcinoma of the urethra. This case brought to 6 the total number of cases of adenocarcinoma of the urethra reported in the literature (table 1).

CASE REPORT

A. W., a 55-year-old Negro, was first admitted to the Hillman Hospital on July 26, 1935, at which time a large peri-urethral abscess was incised and drained. He gave a history at that time of having had a similar abscess incised and drained in 1918 and again in 1926. There was no history of urethral dilatation following the operation in 1935.

On August 29, 1949, the patient returned to the urology clinic having been relatively asymptomatic for 14 or 15 years until July 1949. At this time he had

mucosa with no evidence of tumor or ulceration. A small stone was visualized lying on the floor of the bladder. A roughened, reddened, irregular area was seen in the urethra just outside of the prostatic portion in the approximate region of the membranous urethra.

Five weeks after admission, under intravenous sodium pentothal anesthesia, the perineal mass was excised. The neoplasm was found invading the left corpus cavernosum, and approximately 4 cm. of the urethra external to the triangular ligament was involved in the neoplastic tissue. The mass was excised as completely as possible removing approximately 8 cm. of the urethra; although it was never felt that it had been removed entirely. A splinting catheter was inserted into the bladder bridging the defect in the urethra. The wound was closed in one layer with drainage.

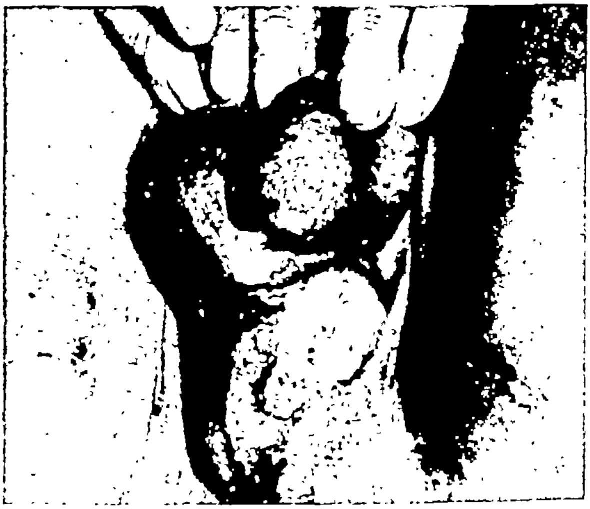

FIG. 1. Gross appearance of neoplasm showing perineum extensively involved by ulcerating, fungating lesion. A large fistulous opening was present in perineum to left of midline.

Convalescence was uneventful and the perineum healed rapidly with minimal drainage. The patient was discharged from the hospital on the eighteenth postoperative day wearing an indwelling Foley catheter.

The gross specimen consisted of a mass of tissue, triangular in shape, with a tube-like structure leading from the base. The base measured approximately 6 by 3 cm., and the specimen measured approximately 5 cm. from base to apex. The tube-like structure projected approximately 3 cm. below the base. When this tube was opened it had all the appearance of a urethra running through the base of the mass and measuring approximately 8 cm. in length. At one point the surface of the urethra appeared to be ulcerated, and a section through this area revealed dense, indurated tissue deep to the urethra. In this firm portion of tissue there was a small cavity approximately 4 mm. in diameter containing yellow mucoid-like material. Gross diagnosis: Adenocarcinoma in the perineum.

Throughout all microscopic sections were present many gland-like structures

variation in nuclear size with so many mitoses and such a tendency to complicated arcade formation of the glands that there was little doubt that it was an adenocarcinoma. There was a strong resemblance to large bowel adenocarcinoma (fig. 2, *B*).

The patient was followed in the urology clinic at weekly intervals. The catheter was removed at the first visit and the patient was able to void without difficulty and without perineal drainage. The urethra was dilated with difficulty at weekly intervals, and, during the sixth week after operation, he began again to drain urine and purulent material from an opening in the perineum. The neoplasm rapidly recurred, attaining its previous size within a short time. Proctoscopy and barium enema 3 months following operation again failed to reveal any evidence of neoplasm within the colon. He was last seen in the urology clinic on April 5, 1950, at which time he refused further surgery.

On April 6, 1950, the patient was admitted to the Veterans' Administration Hospital at Tuskegee, Alabama where he expired 1 month later. Permission for a postmortem examination was not obtained.

DISCUSSION

A knowledge of the embryological development of the urethra and bladder is essential to an understanding of the development of neoplasms occurring in these locations. The first step in the development of the urethra is the formation of a cloaca which is formed when the hindgut fuses with the ectoderm of the caudad portion of the ventral body wall. This fusion results in the formation of a cloacal membrane which persists for some time. At approximately the 5-6 millimeter stage of embryonic development the cloaca is divided into a ventral and dorsal portion by the caudad migration of the cloacal septum. The ventral portion of the cloaca is then incompletely divided into a superior segment representing the bladder and urethra and an inferior segment, the urogenital sinus. As the above changes are occurring the genital tubercle arises on the ventral body wall immediately superior to the urogenital membrane. The latter structure comes to lie on the rectal surface of the genital tubercle or phallus as the latter enlarges. At this stage a phallic portion and a pelvic portion of the urogenital sinus can be recognized. From the pelvic portion the prostatic and membranous urethras develop while the more distal urethra develops from the phallic portion.

The prostatic urethra is lined by a transitional type of epithelium varying in thickness from 3 to 5 layers of polygonal, cuboidal, or low columnar cells. The membranous urethral epithelium is similar to that of the prostatic urethra except that there are scattered areas of squamous cells. Stratified columnar epithelium lines the distal urethra varying in thickness from 2 to 5 cells.

The epithelial lining of the urethra is subjected to various types of trauma. Stricture of the urethra is probably the most common of these. The close relationship between urethral stricture and the development of carcinoma of the urethra has been commented on many times. The usual direction of the change occurring in the urethral epithelium as a result of chronic irritation is toward the development of a stratified epidermoid type of epithelium. When neoplasm ensues, the

the epithelium of the male urethra is complicated by the presence of the glands of Cowper and Littre from either of which gladular tumors may arise. However, the histologic appearance of carcinomas arising in these glands is not similar to those arising as a result of glandular metaplasia of the urinary epithelium. As previously stated these have a close resemblance to large bowel adenocarcinoma. No detailed description of the histology of the tumors originating in the glands of Littre accompanies the cases reported. Gutierrez describes in detail the microscopic appearance of his reported case of adenocarcinoma of Cowper's glands. This neoplasm was characterized by many areas of large acini filled with epithelial strands and other areas of small regular acini lined by large glandular cells. It is evident that, in the case of adenocarcinoma of Cowper's glands at least, there should be no confusion with adenocarcinomas arising from the urethral epithelium.

Foot mentions one case of adenoma of the prostatic urethra and a second case in which glandular epithelium with branching glands was found in fragments resected transurethrally from the prostatic urethra. He states that metaplasia toward a glandular type of epithelium can occur at any point from the kidney pelvis to the prostatic urethra and may even occur in the penile urethra.

The exact site of origin in most cases of urethral carcinoma is impossible to determine because the usual delay in making a correct diagnosis results in fairly widespread extension of the tumor with obliteration of the primary site as well as contiguous structures. Thompson reported a case of an adenocarcinoma of the rectum involving the penis, postulating that it had invaded the penis by direct extension. The unusual histologic appearance of the neoplasm in the case presented stimulated numerous attempts (repeated proctoscopies and barium enemas) to find a primary site in the colon. There was no indication of a rectal origin. No evidence of tumor was found in the bladder on cystoscopic examination; however panendoscopic examination of the urethra revealed neoplasm involving the portion immediately distal to the prostatic urethra. In view of the failure to find a point of origin elsewhere, and because of the striking similarity to adenocarcinomas which very occasionally arise at other sites in the urinary tract, it is assumed that this neoplasm had its origin in the urethra.

SUMMARY

A case is presented in which an adenocarcinoma originated in the urethra, probably as a result of metaplasia of the urethral epithelium.

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CARCINOMA IN DIVERTICULUM OF FEMALE URETHRA

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Diverticulum of the female urethra was not commonly referred to in the literature 15 and more years ago, but since then many reports on the subject have come into the record. Primary carcinoma of the female urethra, like that of the male, is an expanding topic, there being more reports of its instance in recent years than formerly. The appreciation of the possible existence of these lesions and the more prevalent use of the panendoscope doubtless explains their more frequent detection. We have not, however, been able to find in the literature a single instance of the simultaneous co-existence of a diverticulum of the female urethra and a primary carcinoma, nor of a carcinoma in a diverticulum (either sex). Doubtless this must have occurred, but we have been unable to find mention of it. It is not the purpose of this paper to give a comprehensive review either of female urethral diverticulum or carcinoma of the urethra, but to report a diverticular carcinoma.

Brack in his excellent recent article on carcinoma of the female urethra, makes no mention of co-existing diverticulum or carcinoma in diverticulum in any of the 338 cases of carcinoma reported to date. Counseller and Cook in separate reports of the 71 instances of diverticulum of the female urethra detected at the Mayo Clinic report no carcinoma, nor do Engel or Higgins in their separate and less recent articles dealing with the subject in patients at the Cleveland Clinic. Wharton, in a contemporary comprehensive report (1950) of the 39 cases of diverticulum of the female urethra at the Johns Hopkins Hospital between 1890 and 1949, gives an exhaustive study of female urethral diverticula, including many complications but makes no mention of carcinoma.

Although it is not the purpose of this report to deal with the subject in males, it is interesting to note that urethral diverticulum with carcinoma has likewise not been reported. Pate recently discussed urethral diverticula in paraplegics, and in his study reviewed the 197 recorded instances of diverticulum of the male urethra. No incidence of carcinoma was mentioned. Some time ago we had occasion to review the literature of primary carcinoma of the male urethra and found no instance of its existence in urethral diverticulum.

Wharton gives an excellent discussion of female urethral diverticula. He found that the size varied from 3 mm. to 8 cm. The wall of the diverticulum was thick if infected, as so many are. The surface membrane layer, if present, was of cuboidal or squamous epithelium. Two diverticula might be present in the same urethra. No co-existing vesical diverticula were found. All diverticula connect with the vaginal aspect of the urethra and may open into any part of the urethra and may have multiple orifices. Calculi, single or multiple, were present in 10 per cent. Spontaneous fistulas into the vagina were rare, though they have been reported following operation. Arthritis was relieved in 1 case by removal of a diverticulum from which gonococci were recovered.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 16, 1951

the midline, a little closer to the vesical orifice than to the meatus. Mucoid tumor tissue was seen inside the sac. Loop biopsy was done without the use of any current. This showed a grade 1 transitional cell carcinoma. The patient was dismissed on November 18 to re-enter later for operation. No indwelling catheter had been used up to that time.

On November 21 she was re-admitted because of retention and severe hematuria. Two hundred and fifty cubic centimeters of clots were evacuated through the sheath of the electrotome and another biopsy done which showed a grade 3 transitional cell carcinoma. Thirty cubic centimeters of mucoid tumor tissue were extruded through the meatus by pressure on the vaginal side of the mass. The mass thus collapsed, but the vaginal integrity did not. An indwelling catheter was inserted and no further bleeding ensued. Operative removal was elected, the diagnosis being carcinoma in a urethral diverticulum. The patient was warned that she might become incontinent.

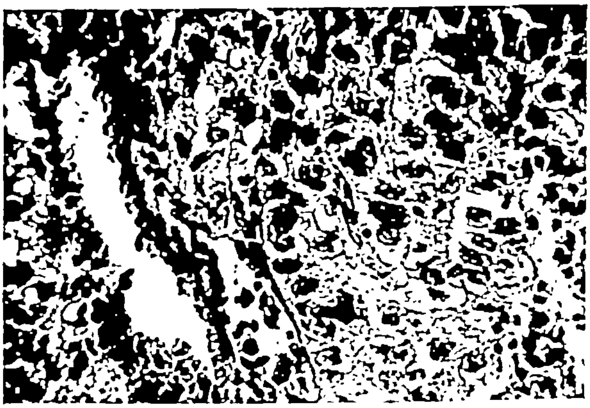

FIG. 1

On November 25, under spinal, pentothal, N_2O and O_2 the patient was placed in lithotomy position, vagina prepared, and further examination showed that the maximum bulge was apparent 1.5 cm. behind the meatus as a result of the collapse a few days before. Vaginal examination above the mass and bimanually was not remarkable. A linear incision about 4 cm. long was made over the bulging mass with division of the anterior vaginal wall. The diverticulum was dissected free from its surroundings and inadvertently opened on its vaginal aspect. Excision of the sac from the urethra left a considerable defect on the urethral floor very close to the bladder. This was closed with interrupted sutures in two layers. A 22F Foley catheter was anchored. Inspection of the specimen revealed it to be 3.7 by 2.8 by 0.8 cm. in size. The wall was not over 1.2 mm. thick. The lining epithelium was red in color, the rest of the sac being fibrous and smooth muscles fibres. There was low grade inflammatory infiltration, and in one area the stump of a previous neoplastic growth, section of which showed dark staining cells of large size penetrating into the muscular walls. No mucoid material was found in the sac after its removal as had been before. Final pathologic report of the removed sac by Dr. Horace Banks was "transitional cell carcinoma of urethral diverticulum (fig. 1)."

The patient had an uneventful afebrile convalescence. The catheter was removed on December 12, having been in 17 days. The patient had good control and was not incontinent. On December 16 vaginal examination revealed no further bulge. She was dismissed on December 17, twenty-two days after operation. Previously mentioned secondary anemia was corrected by transfusions though the hemoglobin was only 9.4 gm. at time of operation. Six months later it was 12 gm.

On January 3, 1950 the patient was seen at our office and a crypt found on the anterior vaginal wall at the site of operation too deep to be seen without a speculum. Urethroscopy on January 11 showed a urethrovaginal fistula just distal to the vesical orifice. No tumor was apparent. The urethral meatus remained very large, being a perpendicular slit 1 cm. long or more. Vaginal examination was normal (except for defect in floor of urethra) save for beginning stenosis of the vault which made the cervix hard to feel. The cervix and uterus were normal. Urinary control was excellent.

On February 28 the patient had a little stress incontinence, worse at night. On May 10 this had improved. The patient urinated without pain and in normal habit. There was no further bleeding. By this time the cervix could not be seen or felt, the upper vaginal vault apparently being closed.

On June 22 vaginal examination with a No. 28 panendoscope showed a small aperture not over size 5F, leading to the upper vault. Urethroscopy showed the urethrovaginal fistula and nothing else.

On July 14, under pentothal, the vaginal adhesions were cut by Dr. J. K. Berman and the vagina opened. Granulation tissue was sectioned and showed no carcinoma. The cervix and uterus were normal. The vagina was dilated and packed with vaseline gauze which was removed a few days later. Urethroscopy was repeated with the same findings as previously.

On December 5 examination showed only the fistula. Urinalysis was normal. A little nocturnal stress incontinence remained.

SUMMARY

Diverticulum of the female urethra was recorded in volume 1 of the *Index Medicus* and thereafter but more frequently in recent years. Carcinoma of the female urethra now has been reported 338 times. No instance of carcinoma of a female (or male) urethral diverticulum has been found in the literature. A case of transitional cell carcinoma in a diverticulum of the female urethra is reported.

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OBSERVATIONS ON HEMOLYSIS DURING TRANSURETHRAL RESECTION: THE EFFECTS OF UREA

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The use of isotonic irrigating solutions has influenced the morbidity and mortality of transurethral resection of the prostate so favorably as to justify just one more report. Isotonic solutions are used for the following reasons.

Instant hemolysis accompanies the mixture of a small amount of blood with a large amount of water, and can be seen to occur during transurethral resection. The venous drainage of the prostate is very rich, as every retropubic prostatectomist knows. The largest veins are in and on the periphery of the prostate, and contain blood at very low pressure; they are necessarily cut at many points during an adequate resection.

That vesical contents enter the circulation during transurethral resection is proved by the following data:

1) Hemoglobinemia is common after transurethral resection with water. The free hemoglobin of the plasma postoperatively averaged fifteen times the preoperative level (Creevy). The postoperative level exceeded 51 mg. per cent in from 17 (Bunge and Barer) to 25 (Goodwin et al.) per cent. Hemoglobinemia does not occur when an isotonic irrigating fluid is used (Creevy, Nesbit, Goodwin et al., and others).

2) The blood sugar remains constant during transurethral resection with water, but rises to 2.4 times the preoperative level when four per cent glucose is used (Creevy). The rise in blood sugar is proportionate to the irrigating pressure (Jessop and Lane).

3) If the bladder is distended with neo-iopax for 5 minutes just after resection, then drained, and an x-ray film exposed 15 minutes later, a urogram will result if the renal function is adequate (Wear).

4) Bacteremia has been observed at the conclusion of transurethral resection in 60 per cent of 360 consecutive cases (Feeney and Creevy). Merritt found bacterial endocarditis 8 times in 7000 consecutive transurethral resections, and in 10 per cent of those with cardiac valvular disease who had prostatic resection.

The writer has been inclined to attribute the hemoglobinemia to blood hemolyzed in the bladder and driven into the circulation, because of the known tolerance of the normal dog and human to considerable quantities of intravenously injected distilled water (100 cc per kilo in the dog—Maluf). However, [illegible], Warren, and Vest have measured the amount of free hemoglobin in the irrigating water used during resection, and have calculated that this could produce a maximum of 116 mg. per cent of free hemoglobin in the plasma. They have concluded that intravascular hemolysis must also be a factor in the hemoglobinemia.

Read at annual meeting, American Association of Genito Urinary Surgeons, Skytop, Pa., May 16, 1951

The effects of hemoglobinemia are well known from intensive studies of the "transfusion kidney." They include pigmented casts in the tubules and degenerative changes ranging from swelling and vacuolation to necrosis of the epithelium of the distal nephron (Lucké) or of the whole nephron (Bell). Identical changes occur after transurethral resection with water (Creevy, Goodwin et al., Credle et al., and others).

The mechanism which produces these changes is not clear. Baker and Dodds believe that the pigmented casts consist of acid hematin formed when the hemoglobin enters the acid urine of the tubules, which are thereby plugged. Since the experimental conditions on which these conclusions are based are highly artificial, and since the number of casts seen in many fatal human cases is too small to plug any considerable proportion of the nephrons, it seems more likely that the vascular spasm which signals the arrival of free hemoglobin in the kidney (Levy; Hesse and Filatov; Mason and Mann) damages the tubules by depriving them of oxygen (Maegraith, Havard, and Parsons). Anuria appears to result from complete reabsorption of the urine by the damaged tubular epithelium or by the interstitial tissue (Dunn, Gillespie, and Niven).

The symptoms of hemolytic reactions are well known; they include chills, cyanosis, and semistupor when severe. Anorexia, nausea, vomiting, oliguria or anuria, anemia and azotemia are common, and are followed by hemolytic jaundice and sometimes by hypertension. Pain in the chest and kidneys is concealed during transurethral resection by the anesthesia, and hemoglobinuria is hidden by the bleeding from the prostate.

The incidence of hemolytic reactions during transurethral resection with water is variable. The writer found postoperative azotemia in 13 of 106 consecutive cases, but only three were seen to be jaundiced and thus almost certainly hemolytic in origin. Goodwin et al. found 5 "lower nephron nephroses" in 69 cases. Two were fatal. This represents between 3 and 7 per cent of severe reactions.

In addition, several factors associated with surgery may reduce the renal blood flow. Van Slyke et al. have seen cessation of the glomerular blood flow during surgical shock; Phillips et al. and Corcoran and Page have produced azotemia by bleeding dogs while maintaining blood pressure by administering fluids. Amorso has caused renal ischemia by distending repeatedly hollow viscera (uterus, bladder) in the experimental animal (Franklin). Sudden bacteremia may certainly cause renal vasospasm and injure the tubules directly as well.

Thus it is certainly a question of the free hemoglobin reaching, not a normal kidney, but one damaged by pre-existing disease and sensitized by acute impairment of its circulation and, at times, by sudden bacterial invasion. Extremely high levels of hemoglobin would appear to be unnecessary in such circumstances.

Since there is no dependable treatment for hemoglobinuric nephrosis, prevention is the obvious solution. That this may be achieved by the use of isotonic solutions of poor electrolytes has been proved by Creevy, by Nesbit, by Garske et al., by Goodwin et al., and by others. Four per cent glucose, 1.1 per cent glycine, and 3 per cent mannitol are equally effective.

Ebert has suggested the use of 1.8 and later of 0.9 per cent urea, alleging that its hemolytic properties, which are well known, are of no consequence. Crelle, Warren, and Vest have seen severe hemolysis follow its use. We have used it ten times at the University Hospitals, but have desisted because there was demonstrable hemolysis (25 to 250 mg. per cent—average 65) in every instance and, because one patient died of a hemolytic reaction, the residents then balked. It is impossible, therefore, to accept Ebert's conclusions. Perhaps his resections are more conservative than ours?

Objections to and substitutes for isotonic solutions have been suggested. It has been alleged that hemolysis can be prevented by using a "low" irrigating pressure. Since the pressure in the pelvic veins is very low, a pressure lower than that would not clear away arterial bleeding: one could not see.

It has also been suggested that one should stop operating when water is seen to enter the cut veins. This is wholly impractical, since the event may be overlooked, and since the use of isotonic fluid obviates interrupting the operation.

It has also been said that the solutions coat the lenses and interfere with vision. This does not occur if the instruments are washed between operations.

Rolnick et al. have claimed that the isotonic solutions blur vision so much that operation is impractical. It is true that blood forms a transparent solution with water and a translucent one with isotonic agents, but one soon learns to compensate for this by holding the lens closer to the objective. Our residents do not appear to be handicapped while learning the operation with isotonic agents.

Periodically someone says that there must be "some other factor than hemolysis" concerned in these reactions. Burning by diathermy is mentioned, but the burn is too small to produce significant hemolysis, since the use of isotonic solutions prevents hemolysis despite the use of diathermy.

Most conclusive proof of the value of these solutions is to be found in the satisfying reduction of mortality which has accompanied their use. Two associates (E. A. Webb and B. A. Smith, Jr.) and I have performed transurethral resections with isotonic irrigating fluid in 1273 consecutive patients between July 1946, and March 15, 1951. Nine deaths occurred in the hospital (0.7 per cent). The last 3 deaths occurred between 40 and 55 days after operation from coronary thrombosis. One was in the hospital continuously because of cardiac decompensation (C.D.C.); the other two had returned because of late postoperative bleeding and then succumbed (E.A.W. and B.A.S.).

During this same period the residents at the University Hospital have operated upon 744 patients with 16 deaths (2.2 per cent) while learning the operation. This makes a total of 2017 cases with 25 deaths or 1.23 per cent.

CONCLUSIONS

The use of isotonic irrigating fluid during transurethral prostatic resection has, by preventing hemolysis, yielded a *striking reduction of mortality* (0.7 per cent in 1273 consecutive cases by experienced resectionists).

The use of urea as an irrigating fluid appears to be dangerous because of its hemolytic properties.

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SQUAMOUS METAPLASIA OF PROSTATE FOLLOWING ESTROGEN THERAPY

A. R. BAINBOROUGH

For a long time it has been known that the prostate is influenced by deviation from the delicate endocrine balance that exists in the body normally. Hence, it has been postulated that certain hormonal disturbances provide the proper environment for the development of prostatic carcinoma and conversely by changing this environment, the cancerous course may be retarded. For a decade now men with carcinoma of the prostate have been treated with female hormones with some extension of life and amelioration of symptoms.

The changes effected in the prostate have been studied sporadically and several excellent papers have appeared, in which the histological changes have been described. By special stains, changes in cellular chemistry have also been observed. For instance, using Gomori's stain, Fergusson found an increased concentration of acid phosphatase in prostatic carcinoma and a disappearance of the acid phosphatase from the prostatic tissue following estrogen therapy.

The histological changes described are briefly:

1) A decrease in the size and number of the cells.[1, 2]

2) Pyknosis and karyolysis of the nuclei.[2, 3]

3) Vacuolation of the cell cytoplasm.[2, 3, 4]

4) Loss of adenocarcinomatous characteristics with adoption of a scirrhous form.[1]

A description of squamous metaplasia of the prostatic glands, following estrogen therapy has not appeared, as far as we know, though it has been described accompanying infarctions of the prostate[5, 6] and occurring independent of other changes.

TABLE 1

CASE	AGE	CLINICAL DIAGNOSIS	HISTOLOGICAL DIAGNOSIS	TREATMENT	INTERVAL BETWEEN TISSUE STUDIES	HISTOLOGICAL APPEARANCE FOLLOWING TREATMENT
1	67	Carcinoma of prostate	Hypertrophy of prostate. No evidence of malignancy. No metaplasia.	Stilbestrol for 2 years	2 years	Squamous metaplasia of prostatic urethra and most of prostatic glands. Still no evidence of malignancy.
2	71	Carcinoma of prostate with bony metastases.	No tissue removed.	Stilbestrol 15 mg. daily for 5 months.		Carcinoma of prostate. Metaplasia of isolated patches of prostatic urethra, some clumps of prostatic glands and a few peri-urethral glands.
3	71	Carcinoma of prostate	Hypertrophy of prostate. No evidence of malignancy. No metaplasia.	Stilbestrol for 11 months	11 months	Squamous metaplasia of prostatic urethra, peri-urethral glands and prostatic glands. Still no evidence of malignancy.
4	80	Carcinoma of prostate. X ray evidence of bony metastases 5 years before death.	No tissue removed.	Orchiectomy 5 yrs before death. Estrogen therapy for 1 to 2 weeks, on 2 occasions 4 & 3 yrs. before death & then constantly for 8 mos. before death.		Autopsy revealed anaplastic carcinoma of prostate. Metaplasia of prostatic glands with some cornification of cells. Metaplastic changes in nonmalignant areas.

denocarcinoma of prostate. No metaplasia	Stilbestrol 15 mg. daily for for 21 days.	27 days	Adenocarcinoma of prostate with classical estrogen effect plus squamous metaplasia of prostatic glands in both areas of malignancy and benignity, and prostatic urethra.
tissue removed	Stilbestrol 15 mg. daily for 22 days.	22 days	Carcinoma of prostate with classical estrogen effect plus squamous metaplasia of prostatic glands in both malignant and nonmalignant areas. No acid phosphatase in metaplastic epithelium, though there was some demonstrable in glands with hyperplastic epithelial lining.
enocarcinoma of pros- ate	Orchiectomy, stilbestrol for 28 mos.	28 mos.	Squamous metaplasia of prostatic urethra, periurethral glands and prostatic glands. Areas of malignancy had undergone a transformation from adenocarcinoma to squamous cell type.

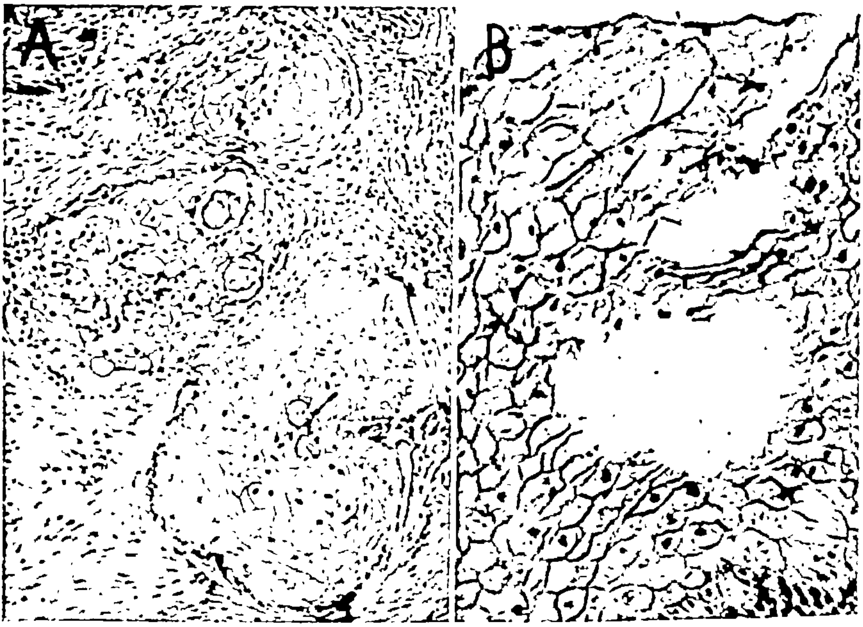


Fig. 1. Case 1. *A*, squamous metaplasia of prostatic glands after 2 years of estrogen therapy. *B*, prostatic urethra in which squamous metaplasia has occurred following administration of stilbestrol for 2 years.

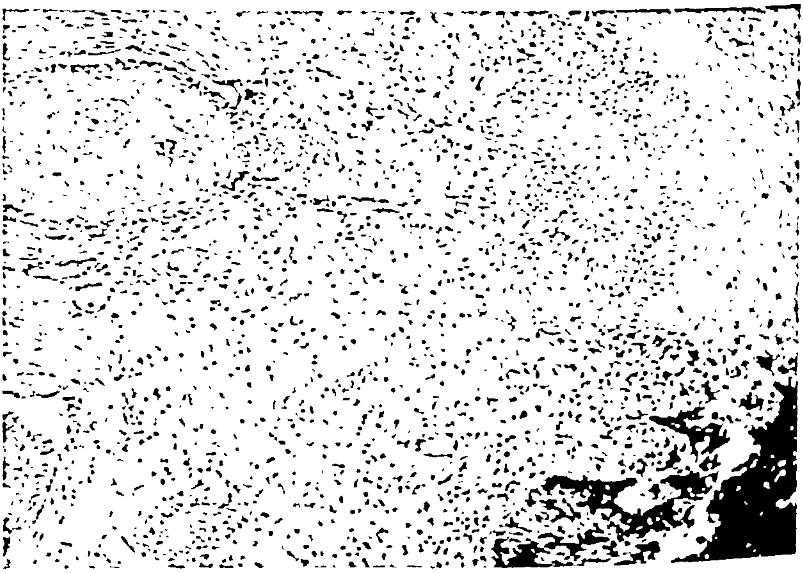


Fig. 2. Case 1. Squamous metaplasia of prostatic urethra and peri-urethral glands after 2 years of estrogen therapy.

plasia in these 4 cases could be the result alone of a reparative process following the previous resection. The hormonal therapy seems to have played some part in the production of the metaplasia.

From the microphotographs (figs. 3 and 4) it is evident that the tall columnar epithelium lining the prostatic glands has been replaced by cells of a stratified squamous or pavement type. In case 4, there was actually some cornification. Nevertheless, intercellular protoplasmic bridges or prickles could not be satis-

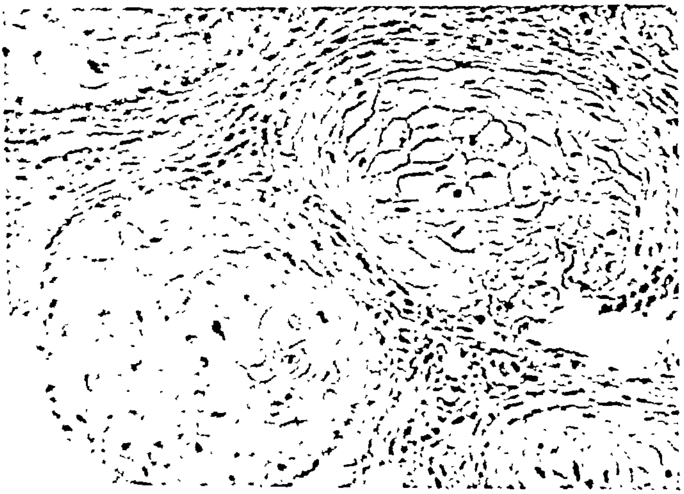
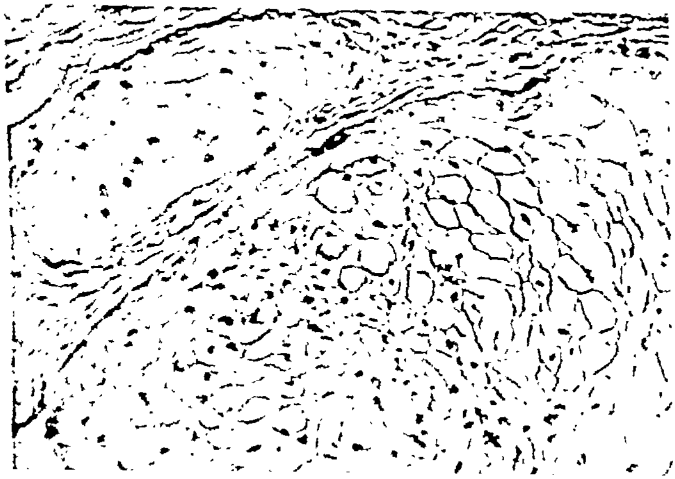


FIG. 3. Case 2. Squamous metaplasia of prostatic glands after 5 months of stillbestrol therapy.



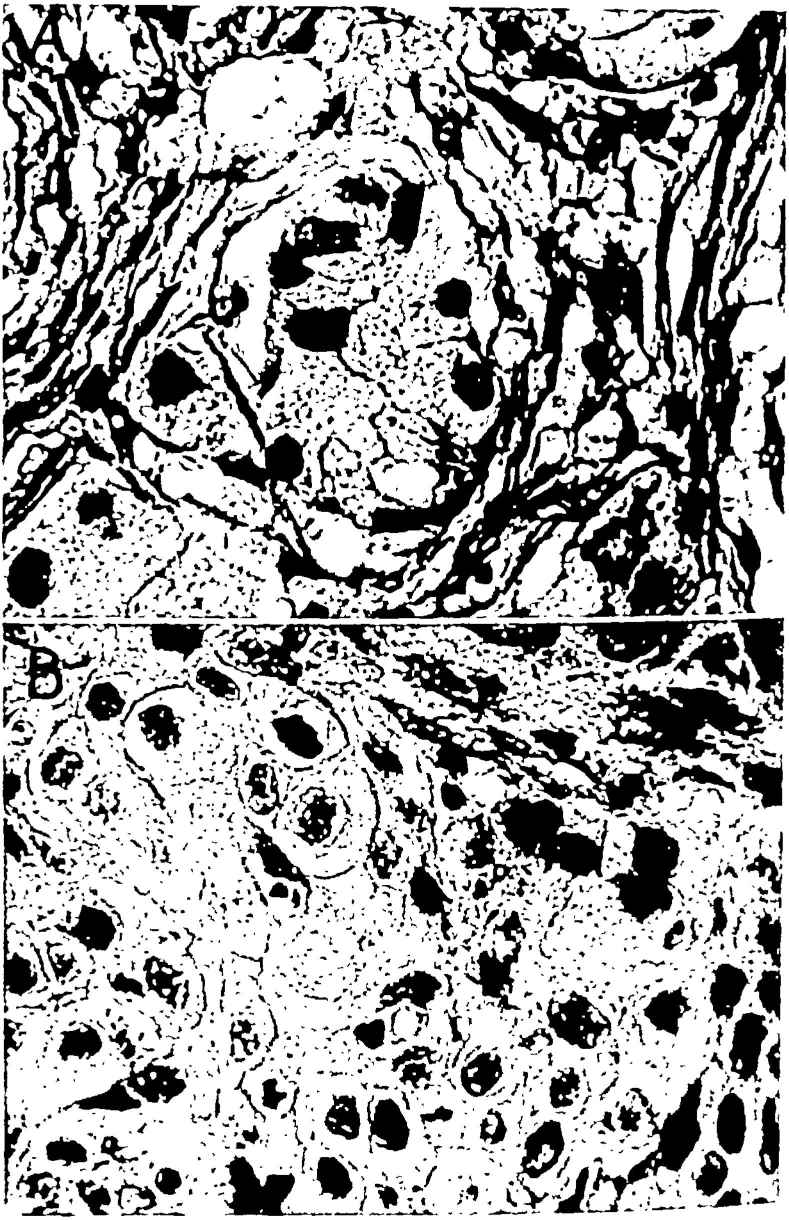


FIG. 5. Case 7. *A*, section showing adenocarcinoma of prostate before intiation of stilbestrol therapy. *B*, carcinoma of prostate, squamous cell type, after 28 months of estrogen therapy. Before treatment, tumor was of adenomatous type. (See *A*.)

latter (case 5). In case 7, even the cell type of the carcinoma had changed, an adenocarcinoma having become replaced by a squamous cell type of malignancy (fig. 5, *A* and *B*).

Many of the cells in the metaplastic areas were vacuolated. In sections stained

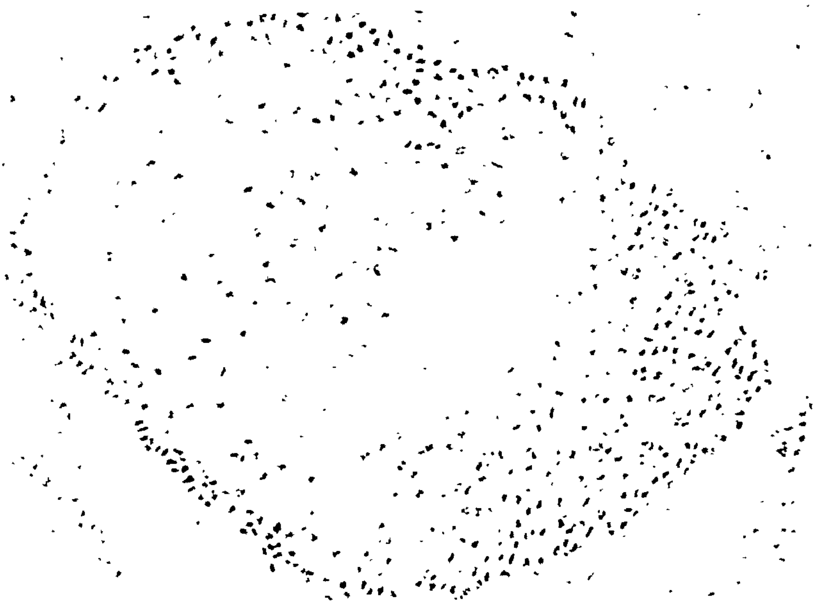
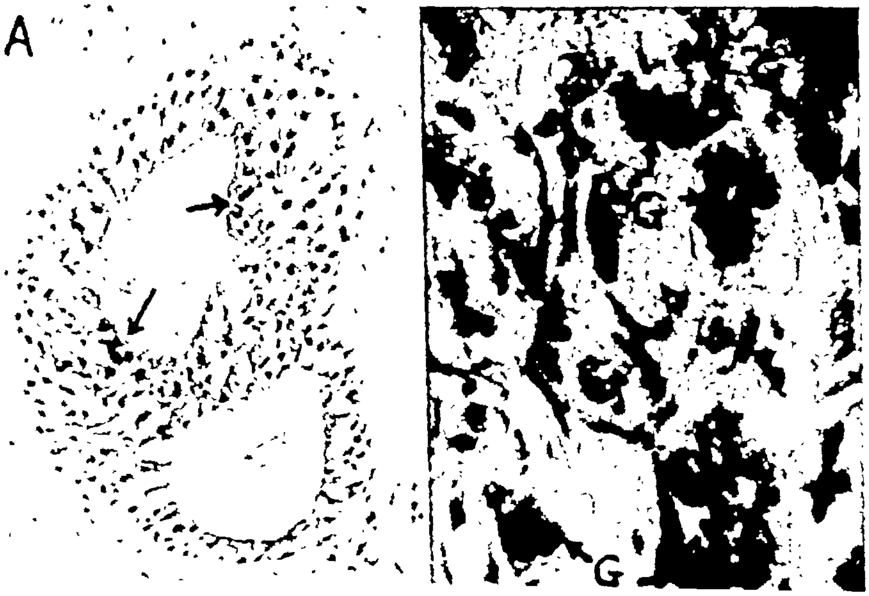


FIG. 6. Case 5. Prostatic glands with squamous metaplasia. No acid phosphatase within these cells.



according to Gomori, the squamous cells were found completely free from acid phosphatase (fig. 6), though in certain areas of hyperplasia, some of the enzyme still remained after stilbestrol administration (fig. 7, *A*). Sudan IV stain likewise showed an absence of fat. Sections stained by Best's carmine revealed glycogen to occupy a position within the cytoplasm corresponding to the vacuolation (fig. 7, *B*). There was no glycogen in cells, other than squamous type. This glycogen content was reminiscent of the increased glycogenation of cells occurring in the squamous epithelium of the cervix associated with endometrial hyperplasia and probably the result of hyperestrogenism.[7]

The necessary duration of estrogen therapy for squamous metaplasia to occur is not known. The shortest interval between the introduction of treatment by hormones and the finding of squamous metaplasia was 22 days (case 6).

We have found no association between liver disease with failure to detoxify the estrogens and the occurrence of squamous metaplasia within the prostate.[8] The number of cases presented here is too small, however, to disregard this possibility in future studies.

There appears to be no particular type of hypertrophy or carcinoma of the prostate that is predisposed to squamous metaplasia.

Many causes for squamous metaplasia have been found and the following may be mentioned:

1) Chronic irritation and inflammation. For example, squamous metaplasia in exstrophy of the bladder and squamous metaplasia of the bronchi following bronchiectasis of many years' duration.

2) Vitamin A deficiency. Hence, Wolbach and Howe[9] were able to experimentally produce metaplasia in many different types of epithelium in experimental animals deprived of vitamin A.

The cause of the metaplasia in the prostate is still obscure. Any theory advanced must account for the common association of metaplasia with infarction of the gland and its frequency, yet inconstancy, following estrogen therapy.

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[7] Bainborough, A. R.: Am. J. Obst. & Gynec., **61**: 331, 1951.

[9] Wolbach, S. B. and Howe, P. R.: J. Exper. Med., **42**: 753, 1925.

[8] Since this paper was submitted, Bennett, Baggenstoss and Butt (Am. J. Clin. Path., **20**: 814, 1950) have described the occurrence of transitional epithelium in the prostates of men dying of cirrhosis of the liver.

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THE NAGAMATSU TECHNIQUE APPLIED TO RETROPERITONEAL DISSECTION IN TESTIS TUMOR

BRICE SEWELL VALLETT

The purpose of my paper is to draw your attention to a new extrapleural approach to the kidney devised by George Nagamatsu of New York and to report 2 cases of testis tumor where the technique was applied in radical retroperitoneal gland dissection.

The incision is a dorsolumbar one. The lumbar part of the incision is developed arbitrarily after leaving the superior lumbar triangle and needs little description. The dorsal part will be briefly described.

The incision begins just above the superior border of the twelfth rib at the angle, sweeps upward in a vertical direction just medial to the angle of the ribs ending at the ninth interspace. Returning to the starting point the incision is carried along the superior border of the twelfth rib. The superior lumbar triangle is now identified, the latissimus dorsi is incised parallel to the direction of the twelfth rib ending when the lumbodorsal fascia is encountered. The serratus posticus inferior muscle and those tendinous slips from the sacrospinalis to the lower three ribs are incised. One inch segments are removed subperiosteally from the twelfth, eleventh and tenth ribs medial to their angle. The lumbocostal ligament to the twelfth rib is now divided, and to the eleventh rib if the twelfth rib is rudimentary. It must be remembered that the downward pleural reflection is the same for both a long and short twelfth rib. The external arcuate ligament of the diaphragm is now divided. This will allow the lowermost portion of the diaphragm and its attached costophrenic sinus to swing upward with the flap.

CASE REPORTS

latissimus dorsi muscles were resutured. The abdominal part of the incision was closed from below upward. No drains were used. Convalescence was uncomplicated excepting slight cough for several days. The patient was out of bed on the sixth day and discharged on the seventeenth postoperative day.

The pathologist's note is interesting. The specimen consisted of a horseshoe shaped multiple cystic, yellowish pink mass of tissue with attached blood vessel tissue and attached lymph nodes 23 cm. in length. The main mass of tissue measured 6 by 4 by 3.5 cm.

Microscopic: Sections from the mass reveal adult teratoid structures and malignant teratocarcinoma cells similar to that reported from the left testis tumor. (Whether the tumor tissues are a manifestation of adult completely differentiated teratoid tissues as well as malignant cells or represent a multicentric origin of teratocarcinoma along the germinal ridge is undecided.) Opinions vary equally. It is difficult to explain metastasis of adult tissue but all references checked refer to the occasional occurrence of this phenomenon.

Case 2. A 34 year old man had had for 7 or 8 years an enlarged, hard, painless right testis which in the 24 hours preceding admission to the hospital had suddenly become painful. A diagnosis of testis tumor was made and a scrotal orchiectomy performed, the pathologist reporting embryonal carcinoma. One week later retroperitoneal gland dissection was carried out employing the Nagamatsu technique, as described in the preceding case.

All fatty, lymphatic and areolar tissue was dissected from the region of the right kidney and renal pedicle downward over the aorta, vena cava, common iliac and external iliac vessels. No metastatic lymph glands were found by the pathologist in the specimen resected. Subsequently the original diagnosis was changed to seminoma.

The postoperative course was uncomplicated. The patient was out of bed on the eighth and discharged on twelfth postoperative day.

COMMENT

To quote Nagamatsu: "Resection of portions of the ribs medial to their angles followed by retraction causes the twelfth and eleventh ribs to be pushed upward carrying with them their attached portions of the diaphragm and contained pleura. The tenth rib, which at the same time has retracted upward one interspace at its freed posterior end, is further retracted upward by rotating at its flexible anterior cartilaginous attachment. This elevation of the pleura in an intact manner would not be the result should the segmental resection be made anterior to the angle of the ribs because the pleura would still be attached to the proximal segment and relative motion of the distal and proximal segments would necessitate tearing of the pleura."

Endotracheal anesthesia was used in both the foregoing cases, and is the ideal method of carrying the patient through a somewhat lengthy operation.

The procedure was well tolerated, as manifested by a rather smooth convalescence in our 2 cases. Neither one complained of postoperative pain. There was very little abdominal distention. Deep breathing exercises were encouraged

The ultimate stability of the back is not impaired. Both patients are back at work and have gained in weight.

SUMMARY

According to modern concepts, the extrapleural, retroperitoneal technique of Nagamatsu gives adequate exposure for radical lymphatic dissection in testis tumor.

Two cases of radical retroperitoneal dissection by this technique for testis tumor are herewith reported, both with satisfactory immediate outcome.

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REFERENCE

Nagamatsu, G. R.: J. Urol., 63: 569, 1950.

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TESTICULAR TUMORS: CLINICAL DATA ON 131 CASES

CARL RUSCHE

The analysis of this group of testicular tumors is primarily concerned with an inquiry into clinical aspects: Is there a significant difference in survival among these different histologic types, and if so, is there an assignable cause; is prognosis related to any measurable factor, as age, duration of symptoms, therapy or histologic findings; is cryptorchidism a predisposing factor to malignancy; is radiation advantageous as an adjunct to orchiectomy and if so, which tumors should be radiated; and what is the response of metastatic lesions to roentgen therapy?

Since there is a difference of opinion among pathologists as to a universal acceptance of nomenclature, some explanation of certain correlations between the histology of the tumor and the course of the disease seems warranted.

The complexity of the structure of new growths originating from embryonal tissue of totipotent proclivities and arising from one or more of the three germinal layers, has provoked a varied description and classification of such tumors. Clinically, it has been supposed that one type of cell might predominate and even mask the presence of less conspicuous elements. Under such circumstances, where there has been a variance in the degree of malignancy, the ultimate prognosis and response to therapy could be accounted for on the basis of the more malignant elements.

The past decade has recorded many serious attempts to simplify and to correlate the clinical features of tumors of the testicles with the gross and microscopic structure, and if possible to establish an acceptable criteria for a more uniform system of treatment and a more valid means of determining a prognosis. I have elected to use the classification proposed by Moore and Friedman (fig. 1).

The data for this study were compiled by abstracting the medical records from eight hospitals within the Los Angeles area, upon patients who had histologic diagnosis of a testicular tumor during the period of January 1942 to January 1948. A total of 131 cases was found to have been indexed. The follow-up program in this study closed November 1950. Questionnaires were submitted to attending physicians as to whether roentgen therapy was administered; progress of disease; and the present status of patient. The amount of radiation was obtained from the radiologists. All of the death certificates were verified. At the close of the study there were 8 patients whose present status could not be determined accurately; 3 with a seminoma; 3 with an embryonal carcinoma; and 2 who had an adult teratoma tumor. The total cases, 131, were used in the computations of distribution of histologic types; age incidence; organ involved; undescended gonads; and presenting symptoms. All other analytical procedures

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Acknowledgement for statistical assistance is given Eschscholtzia L. Lucia, Ph.D., Lecturer in Oncology (Biometrics), University of California School of Medicine, San Francisco, Calif.

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were based on the 123 cases with conclusive information as to present status at close of investigation.

Seminomas and embryonal carcinomas occur with greater frequency than other types of histologic entities, and with co-equal incidence in this study (31 per cent). The incidence of adult teratomas (15 per cent), and teratocarcinomas (14 per cent) was also practically equal to each other. True chorio-epitheliomas, the most malignant tumor of the testicle, are rare, and the microscopic sections of this group (2 per cent) were submitted to Friedman for confirmation of diagnosis. The pathologic entities among the benign tumors (7 per cent) were: gumma, fibroma, mesothelioma of tunica vaginalis, fibromas of tunica vaginalis, granuloma, lymphangioma, tubular adenoma, and a cavernous hemangioma (fig. 2).

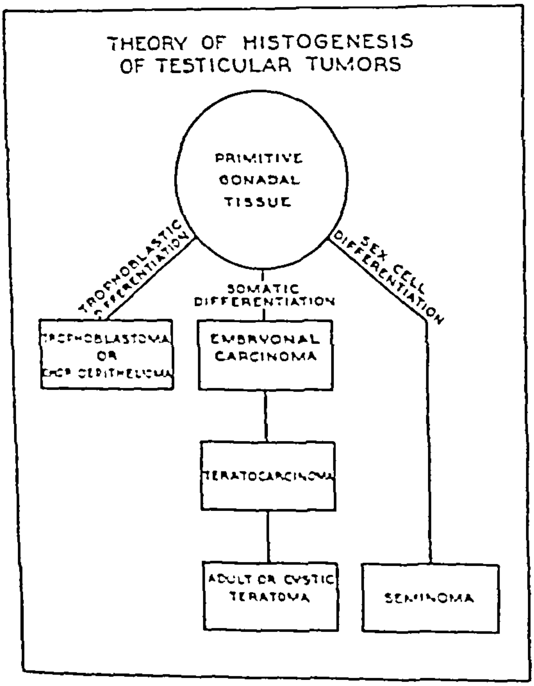


FIG. 1. Theory of histogenesis of testicular tumors

The incidence of testicular malignancy is pre-eminent during the years of maximum sexual activity, with the mean age for the 131 cases being 36 years. The youngest male was 15 and the oldest 77 years of age. There was no significant difference between the mean ages of the group with seminoma (38 years) and the group with embryonal carcinoma (37 years); group with teratocarcinoma (33 years); and the group with adult teratoma (27 years). The three chorio-epitheliomas occurred in patients who were 27, 34 and 51 years of age respectively. Among the eight with benign tumors, the ages ranged between 20 and 70 years.

The [illegible] age distribution of the groups with seminoma and embryonal carcinoma approximate each other rather closely; while that of the group with adult teratoma not only shows a mode in the lower age of 20-29 years, but begins in the earlier age group of 15-19 years and does not extend beyond the 30-39 age group.

The mean ages of this series are slightly higher than those reported by Friedman and Moore (1946), and O'Connell and Geschickter (1950) whose studies were confined to men of military age.

Testicular neoplasms appear to have a predilection for the right testicle, as 81 (62 per cent) of these tumors developed on this side and 50 (38 per cent) involved the left organ, in conformity with previously reported statistics. There was no instance of bilateralism in this series of cases.

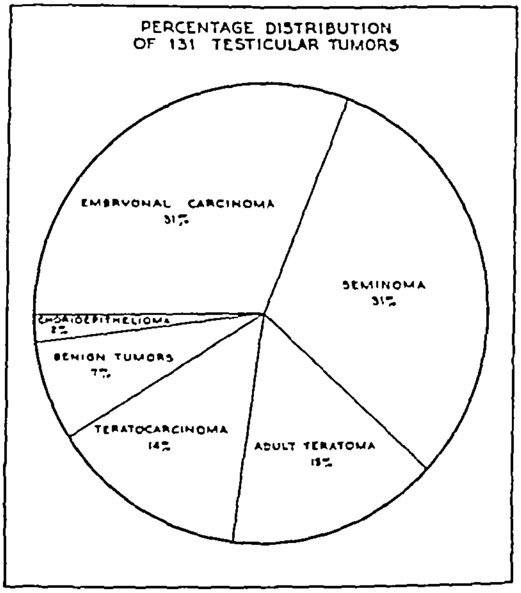


FIG. 2. Percentage distribution of 131 testicular tumors

CRYPTORCHIDISM

Whether a cryptorchid has a greater propensity for the development of malignancy than a normal testicle has been disputed since 1851, when LeComte first asserted that undescended organs frequently became malignant. There always has been a discrepancy among the reports by various writers concerning the actual index of incidence. Campbell (1942), in reviewing the literature, found the frequency of malignant change in the undescended testicle to be high; as did Gilbert and Hamilton in their study (1940). Whereas, Carroll (1949) stated: "The statistical frequency of malignant cryptorchidism will never be amenable to mathematical study until generally accepted accurate data are presented and proven. All past statistical studies on this subject therefore should be disregarded as being definitely open to question."

The potentiality of malignancy in many instances has been the paramount argument for surgical removal of the ectopic testicle. In the same period of years and from the same hospitals, from which the data for this study of testicular neoplasms were compiled, there were 107 undescended testicles surgically removed. Histologic examination of these 107 testes demonstrated the absence of a malignant process in all instances. Of the total, 107, 99 (82 per cent) were associated with a hernia; 19 (28 per cent) were complicated by either a hydrocele, hematoma, torsion, orchitis, hemorrhage, epididymitis, varicocele or spermatocele. The mean age was 32 years for the group of 107 undescended testes which did not become malignant, the age when a testicle is likely to develop malignancy.

In a forthcoming paper dealing with testicular tumors during childhood, I have observed that the maximal incidence is before the third year of life. There was no instance of tumor development in an ectopic organ among these children. Seven of the 12 cases were teratomas; 3 were embryonal carcinoma; and 2 dermoid cysts.

TABLE 1. *Fifteen cases of undescended testes. In 11, tumor developed in abnormal organ, in 4, tumor developed in normal testis in presence of a corresponding ectopic organ classified as to age, type of tumor, and interval between orchiopexy and tumor development*

AGE AT TIME OF DIAGNOSIS	SITE OF ECTOPIC TESTIS	SIDE OF TUMOR	TYPE OF TUMOR	ORCHIOPEXY PERFORMED	INTERVAL IN YEARS BETWEEN ORCHIOPEXY AND DEVELOPMENT OF TUMOR
25	L	L	Seminoma	No	
37	L	L	Seminoma	Yes	3
37	*R*	*L*	Seminoma	Yes	(Tumor in normal organ)
41	*L*	L	Seminoma	No	
43	*R*	*L*	Seminoma	Yes	(Tumor in normal organ)
60	L	L	Seminoma	No	
29	R	R	Embryonal carcinoma	Yes	10
31	*L*	*R*	Embryonal carcinoma	No	
32	L	L	Embryonal carcinoma	No	
29	L	L	Embryonal carcinoma	Yes	5
40	*L*	*R*	Teratocarcinoma	No	
34	R	R	Chorio-epithelioma	No	
29	R	R	Adult teratoma	Yes	7
30	*R*	*R*	Adult teratoma	No	
29	L	L	Tubular adenoma	No	

(1945), there was a greater frequency of malignancy of the right cryptorchid. I found that in 11 of the 15 ectopic testicles which developed tumors, the left organ was involved seven times and the right only four times.

SYMPTOMATOLOGY

There are no discernible pathognomonic symptoms of a malignant testicular tumor. The most distinguishable characteristic is an insidious, painless, local enlargement of the testis. This was present in 98 cases (75 per cent). Tumefaction accompanied by testicular pain has been difficult to evaluate. Two of the 27 patients who experienced testicular pain had benign neoplasms (table 2).

A primary testicular lesion may develop metastatic lesions without early corresponding clinical findings in the testicle. In 5 cases the presenting symptom was a retroperitoneal mass, and for a limited time the primary neoplasm was assumed to be of other than testicular origin. In one of these cases, testicular manifestations did not occur until 8 months after the initial appearance of a retroperitoneal mass. There was also an extraordinary clinical course in a patient, aged 77, who sustained a pathological fracture of the right femur. He presented no evidence of primary neoplastic involvement for 8 months, at which time the right testicle enlarged and palpation revealed a hard, firm tumor mass. Microscopic examination of the surgically removed specimen disclosed an embryonal carcinoma of the testicle The patient expired 3 months after orchiectomy.

TABLE 2. *Initial presenting symptoms of 131 patients with testicular tumors*

	TOTAL (131)	SEMINOMA (41)	EMBRYONAL CARCINOMA (41)	ADULT TERATOMA (20)	TERATOCARCINOMA (18)	CHORIOEPITHELIOMA (3)	[illegible]
Painless enlargement	98	36	28	14	13	1	6
Painful enlargement	27	4	9	6	5	1	2
Retroperitoneal mass	5	1	3			1	
Pathological fracture	1		1				

There were no statistically significant differences in the interval between onset of symptoms and confirmation of diagnosis for the different types of tumors. The duration of symptoms for the entire group ranged from 1 week to 5 years. There were no differences in duration of symptoms among the groups of patients who had metastases at the time of diagnosis, those who subsequently developed metastases, and those who are alive without evidence of disease.

Rapidity and size of the tumor growth varies, and is believed to be of minimal prognostic value. True chorio-epitheliomas, the most malignant of all testicular tumors, are diminutive in size and at times difficult to palpate.

Trauma is not a component in the genesis of neoplastic growth, though its function in the dissemination of existing malignant cells has not been ascertained.

The late James Ewing, pathologist for the Memorial Hospital for the Treatment of Cancer and Allied Diseases, stated: "It is generally assumed that trauma may activate a latent cancer and increase the growth energy of the but the grounds for this view are unsatisfactory. It is doubtful if any primary cancer is ever in a state of quiescence, although the early growth may be slow. The idea that trauma may endow the cells with greater powers of growth must be rejected. The growth energy of tumor cells is determined by the conditions of origin, although its manifestation may vary with the environment . . . Present data confirm the view, long since adopted by pathologists, that a single trauma of normal tissues is incapable of producing a malignant tumor."

Gilbert (1943) cited the 21 cases of testicular trauma which Ewing analyzed from a medicolegal aspect. The possible relation between the trauma and the accelerated growth was accepted in 4 of the cases. The anatomical position of the organ makes it more susceptible to injury, as a tumor may go unobserved until pain is experienced resulting from external violence. Of the 25 patients in this study who associated trauma with the pathologic organ, eleven were concurrent with the onset of symptoms; and the interval of time between injury and the occurrence of symptoms for the other 14, ranged from 6 months to 26 years.

Gynecomastia is usually a manifestation of the disturbance of the hormonal production, and was an uncommon objective finding among this group. The syndrome in this group was associated with seminoma, embryonal carcinoma, adult teratoma, teratocarcinoma, and chorio-epithelioma. It was present in 5 cases at the time of diagnosis, and in one instance developed 1 month prior to death.

DIFFERENTIAL DIAGNOSIS

When testicular palpation reveals a symmetrically enlarged organ, smooth or irregular in shape, from a firm to hard consistency, the presumptive diagnosis should always be malignancy. The only acceptable procedure for confirmation of the diagnosis is an orchiectomy with microscopic examination of the surgical specimen. A biopsy procedure is condemned. The histologic examination of a biopsy specimen in 1 case showed granulomatous tissue; 4 months later extensive metastases had developed. Upon surgical removal of the testicle, the microsections showed a teratocarcinoma. The patient died within 2 months. Ordinarily the tumor affects the body of the testicle; though of the total, 131, there were 19 (14 per cent) with invasion of the epididymis as demonstrated on histologic examination.

The early recognition of these neoplasms may be confusing because of the similarity of symptoms with other scrotal diseases. Sixteen of the 131 patients were incorrectly diagnosed, four received supportive treatment prior to surgical intervention; six were diagnosed as hydrocele, seven as epididymitis, two as strangulated undescended testes, and one as a spermatocele.

Ormond and Best (1948) found the metastatic process to appear earlier in men under 30 years of age. However, I found age to be of no prognostic value among this group. There was a significant relationship between the type of testicular malignancy and the presence of metastases at time of diagnosis: among those with seminoma, 15 per cent showed early dissemination; 26 per cent of the embryonal carcinoma group; 35 per cent with adult teratoma; 42 per cent with teratocarcinoma; and 100 per cent within the chorio-epithelioma group.

It is an axiom that prognosis is greatly dependent upon the presence or absence of metastases. Roentgen therapy appears to have a definite value in some instances where metastases have occurred, as a number of cases have been reported where the disease has been arrested for a considerable period of time by radiation.

There was evidence of roentgenographic regression of metastatic lesions in eight instances of the group which were followed to the close of the investigation. A patient with retroperitoneal involvement from an embryonal carcinomatous tumor, who received 4800r is alive and well without evidence of disease 71 months later. Another patient who presented lung metastases at the time of examination, received 8,850r preoperatively and a total of 21,100r distributed over the thorax, pelvis, and abdomen subsequent to the surgical removal of an embryonal carcinomatous tumor. Within four months the roentgenograms showed regression of the metastatic process, and the patient is known to be alive without evidence of disease 38 months subsequent to diagnosis. Barringer (1944) reported a similar response to roentgen therapy by regression of embryonal carcinomatous metastases, with quiescence longer than has been experienced with other testicular tumors.

An extraordinary convalescence ensued in 1 patient who presented abdominal and mediastinal teratomatous metastases at the time of orchiectomy. A total of 25,000r were administered postoperatively. After 4 years, the patient is well and leading a life commensurate with his age of 31 years.

Friedman (1947) in his histogenetic treatise of testicular tumors, discusses the evolutionary procedure of the differentiating components of germ-cell tumors and their metastatic processes. In his study of 922 cases, 0.4 per cent of the tumors were pure chorio-epitheliomas, with an incidence of 25 per cent of the deceased cases containing chorio-epitheliomatous metastases. In this study, one of the patients with a teratoma tumor was autopsied a year subsequent to orchiectomy; postmortem microsections showed chorio-epitheliomatous metastases of the lungs, adrenal glands, pancreas and kidney. The uninvolved testicle showed hyperplasia of the interstitial cells of Leydig. It is known that interstitial tumors are very rare, though hyperplasia is not uncommon. Prophylactic roentgen therapy may have been the contributing factor in the decrease of spermatogenesis of the remaining testis. Extensive bilateral gynecomastia occurred 1 month prior to death, a syndrome frequently associated with both chorio-epitheliomas and interstitial cell tumors.

LABORATORY TESTS

Gonadotropic hormone in the urine of a host with a testicular malignancy was observed 20 years ago by Zondek, who believed it to be a serviceable diagnostic adjunct. The principle of this test has undergone many modifications with limitations of its usefulness. Francis (1945) believes that with a more strict standardization of technique, the test would be of considerable value.

A negative test does not rule out a malignant testicular tumor. The vast majority of the hormonal bio-assay tests in this group of cases were negative. The infrequent positive reactions were not limited to any one of the pathologic groups.

TYPES OF THERAPY ADMINISTERED

The most efficacious method of therapy for testicular neoplasms remains a controversial subject. Should a simple or a radical orchiectomy be performed; should roentgen therapy be administered to all types of testicular neoplasms, and if so, what is the optimum time and amount to be administered?

Lewis (1948) recommends the Chevassu procedure, which consists of extirpation of testicle, epididymis, spermatic cord, and dissection of regional lymphatics to the renal pedicle, for all malignant testicular tumors other than seminomas. Extensive retroperitoneal lymph gland dissection has had few supporters. Most clinicians advocate a simple orchiectomy, removal of testis and epididymis for all types of tumor. In this study there was no instance of a radical procedure.

The histologic properties of these tumors are believed to respond differently to roentgen rays. Chevassu (1906) disclosed the theory of the radiosensitiveness of seminomas, and the radioresistance of teratomas was evolved by Desjardins, Squire and Morton (1929). Ahlbam (1947) stated: "Our experience is that some tumours belonging to the mixed tumor and adenocarcinoma sub-group have a radiosensitivity which comes very near that of the seminoma."

In Patersons' discourse (1949) on seminoma, he stated: "It is one of the few tumours in which prophylactic irradiation is always indicated, even if there is no suggestion of secondary involvement." Sheetz (1942) in his study of 54 cases of teratoma found them to be extremely resistant to roentgen rays, and determined that a cure was dependent on early orchiectomy. Nesbit and Lynn (1940) advocate prophylactic postoperative radiation for all testicular tumors except chorio-epitheliomas; whereas Riba (1950) advises postoperative radiation for all malignant tumors except adult teratomas.

Proponents for preoperative radiation maintain that roentgen therapy will prevent dissemination of the metastatic cells by sealing off the lymphatics. [illegible] (1950) found that roentgen therapy will alter the histopathologic properties of a tumor and lessen the accuracy of diagnosis. Others believe it is inexpedient to radiate a tumor which has not been examined histologically. One of the patients in this study received 1000r preoperatively and the microscopic sections revealed benign fibromas of the tunica vaginalis.

Inasmuch as the data for this study were compiled from eight different hospitals, there was no standard method of treatment. Thirty-seven of the total group, 131, were treated by orchiectomy only; seven of these were benign tumors. The 88 cases receiving palliative and curative postoperative radiation were proportionally represented among the different histologic types. Metastatic lesions were present in the 4 cases which were radiated prior to orchiectomy; and in two instances, at time of roentgen therapy, the primary lesion was assumed to be of retroperitoneal origin. The clinical course of the chorio-epithelioma which was treated by radiation only did not warrant surgical extirpation; and the postmortem microscopic sections confirmed the clinical diagnosis (table 3).

Supervision of roentgen therapy was not restricted to one radiologist. The theory that certain tumors are radiosensitive and others radioresistant was not observed in all instances, nor was there uniformity in the technique used or total dosage of roentgens administered to the different types of tumors. The variation in time of survival of patients with different tumors, when correlated with the total roentgens, is an interesting observation.

TABLE 3. *Treatment administered to 131 cases of testicular neoplasms*

	TOTAL (131)	SEMINOMA (41)	EMBRYONAL CARCINOMA (41)	ADULT TERATOMA (20)	TERATOCARCINOMA (18)	CHORIO-EPITHELIOMA (3)	[illegible]
Orchiectomy only	37	11	8	7	4		7
Preoperative radiation, and orchiectomy	1						1
Preoperative and postoperative radiation, and orchiectomy	4	1	2		1		
Orchiectomy and postoperative radiation	88	29	31	13	13	2	
Radiation only	1					1	

Seminoma. One patient who received a total of 3000r has lived 105 months; whereas another patient living 70 months had 13,000r. The maximal dosage of 21,000r was administered to a patient with metastatic lesions, who died 37 months following orchiectomy.

Embryonal carcinoma. The 3 patients in this group who received the minimal dosage, 2000r, have lived 81, 83 and 89 months respectively. A patient receiving 24,000r has lived 96 months; and the maximal dosage of 34,000r is correlated with a 59 month survival.

Adult teratoma. The patient of this group who has lived the longest, 96 months, received the minimal dosage, 3000r. The patient who received 25,000r with regression of the metastatic process, as previously mentioned, is still alive at [illegible] months.

Teratocarcinoma. The diagnosis of the patient who has lived 105 months, receiving a total of 11,000r, was confirmed by the Army Institute of Pathology. A patient who received 12,500r has lived 53 months; and the maximal dosage of 17,000r was administered to a patient who died 13 months after diagnosis

SURVIVAL

The time element prevailing between diagnosis and the close of the follow-up program (November 1950) permitted all cases to be followed through the fourth survival period.

Annual mortality rates and successive annual survival rates for seminoma, embryonal carcinoma, adult teratoma and teratocarcinoma were calculated according to month and year of diagnosis, and grouped uniformly as to maximum last year and month of follow-up since diagnosis (table 4). There are nine possible survival periods dependent upon the year of diagnosis; cases diagnosed in 1942 were followed to the ninth survival period; whereas cases diagnosed in 1947 were followed through the fourth survival period. There are three basic

TABLE 4. *Total number of cases of four pathologic entities at risk in each survival year, the per cent mortality in each year and the per cent survivors at the end of each year of the initial total cases in each group*

[illegible]	SEMINOMA			EMBRYONAL CARCINOMA			TERATOCARCINOMA			ADULT TERATOMA		
	Number at risk first of each survival year	% mortality each year, of number at risk	% survivors at end of each year, of initial total at risk	Number at risk first of each survival year	% mortality each year, of number at risk	% survivors at end of each year, of initial total at risk	Number at risk first of each survival year	% mortality each year, of number at risk	% survivors at end of each year, of initial total at risk	Number at risk first of each survival year	% mortality each year, of number at risk	% survivors at end of each year, of initial total at risk
1	[illegible]	16%	84%	38	13%	87%	18	33%	67%	18	17%	83%
2	[illegible]	12%	74%	31	15%	74%	12	42%	39%	15	33%	55%
3	[illegible]	0%	74%	[illegible]	0%	74%	7	0%	39%	10	0%	55%
4	[illegible]	7%	[illegible]	[illegible]	4%	71%	3 (4)	0%	21%	10	0%	55%
5	[illegible]	[illegible]	61%	21 (6)	0%	66%	3	0%	21%	6 (4)	0%	45%
6	[illegible]	0%	[illegible]	12 (9)	0%	52%	2 (1)	0%	15%	6 (3)	0%	27%
7	[illegible]	0%	[illegible]	10 (2)	0%	45%	2	0%	15%	2 (1)	0%	20%
8	4 (1)	0%	25%	5 (5)	0%	33%	2	0%	15%	1 (1)	0%	11%
9	[illegible]	0%	[illegible]	2 (3)	0%	15%	1 (1)	0%	5%	0		

* Numbers in parentheses refer to number of cases known to be alive at the beginning of the highest survival year, [illegible] this year because of the limitation of the closing date of the study

CASE REPORT

A man 27 years of age, with a chorio-epithelioma, when first seen complained of increasing pains in the hips, sacrum, and coccyx following a fall at work 9 months previously. Gross hematuria was the only manifestation of genito-urinary disease, and this occurred 8 months after the onset of the illness.

Physical examination disclosed a firm, fixed mass in the epigastric region, 5 cm. in diameter. A right hernia was present. The right testicle showed atrophy; it was one-half the size of the opposite gland and its consistency was considered normal.

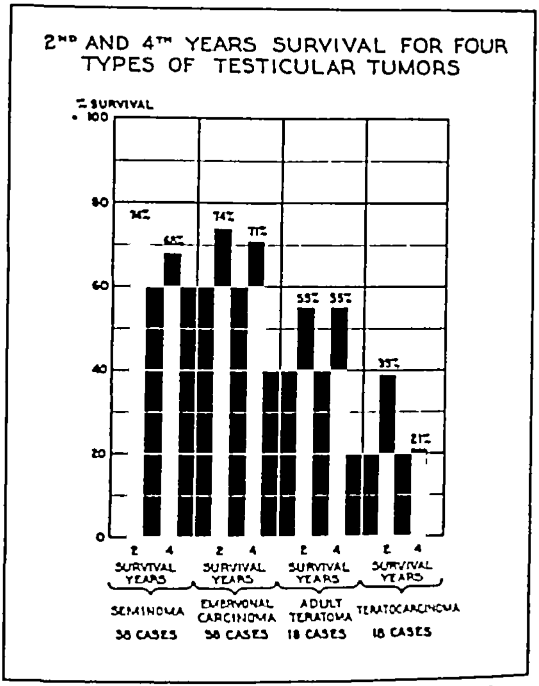


Fig. 3. Second and fourth years survival for four types of testicular tumors

Cystoscopy revealed an ulceration at the dorsum of the prostatic urethra about ½ cm. from the bladder neck. Indigo carmine injected intravenously appeared in good concentration from each kidney. The retrograde pyelograms were normal. Roentgenograms of the lower thoracic and upper lumbar spine disclosed an osteochondritis of the vertebral plates, and degenerative changes of the posterior articulations. Roentgenographic studies of the gastro-intestinal tract revealed a mass in the left upper quadrant, displacing the distal portion of the duodenum and jejunum.

The subjective and objective symptoms were progressive in nature, though there were no manifestations of testicular involvement. Microscopic sections of a biopsy from a right inguinal gland revealed the presence of chorio-epitheliomatous involvement (fig. 4). The primary lesion was assumed to be in the right testicle, but the presence of a tumor mass could not be palpated.

Roentgen therapy was instituted but a very rapid progression of the disease followed. Death occurred 6 weeks subsequent to the appearance of the [illegible] dominal mass. The necropsy examination disclosed a chorio-epithelioma of the right testicle with metastases to the mesenteric lymph nodes, inguinal lymph nodes, liver, spleen, adrenals, pancreas, urinary bladder, ureters and recto-sigmoid. There were two small nodules present in the right testicle, measuring 1 cm. and 8 mm. in diameter respectively (fig. 5). Forcible palpation of this organ

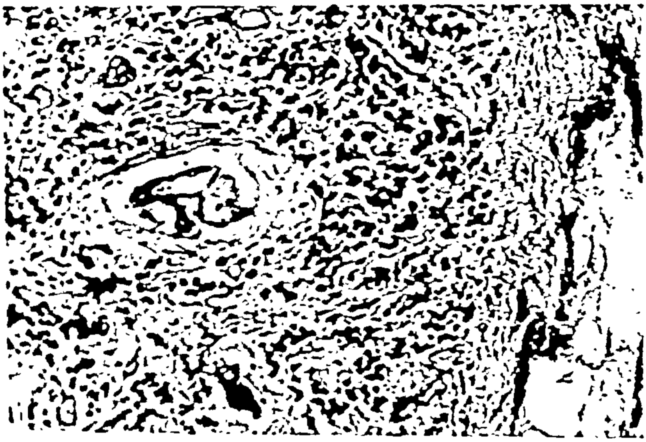
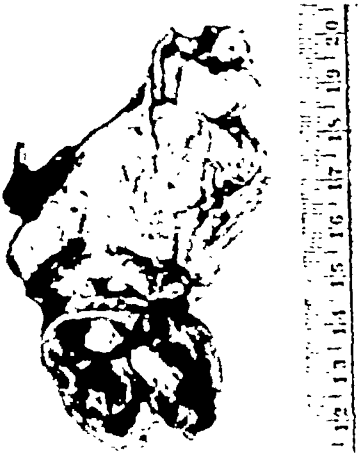


FIG. 4. Chorio-epithelioma showing pale polyhedral cells with large vesicular nuceli and clear to pale cytoplasm (Langhans' cells). Giant cells with multiple, small, oval, dark nuclei of syncytial type. X 130.



with no subjective complaints until pain developed 3 days prior to extirpation of what was assumed to be a teratoma. The histologic examination disclosed a fibroma arising in the region of the rete testis, which is a slow-growing process.

Tubular adenomas are believed to originate from the Sertoli cells and their infrequent occurrence in men, though common in dogs, has been associated with pseudohermaphrodites or cryptorchids. One of the patients in this study had an orchiectomy for an undescended testicle, and the tubular adenoma was an incidental histologic finding.

In two instances, the microscopic examinations revealed the tumors within the tunica vaginalis; one, a mesothelioma; the other, multiple fibroma. Friedman classifies a fibroma of the tunica vaginalis as a pseudo tumor, describing it as an abundance of connective tissue with vessels, calcium, and minimal amount of lymphocytes. Mesotheliomas, a very rare pathologic entity, are also known to occur in the epididymis and fallopian tubes.

COMMENTS

The overall 5-year survival for this series of malignant testicular tumors was 54 per cent. The survival rate may be correlated with the degree of differentiation of the neoplasm, as the 5-year survival rate for seminoma was 61 per cent; embryonal carcinoma 66 per cent; adult teratoma 43 per cent; and teratocarcinoma 21 per cent. The mortality rate was highest during the first 2 years after diagnosis, demonstrated by an overall 35 per cent mortality for this period. The study suggests that when the period of survival is 2 years or more the prognosis becomes more favorable, since the extension of the growth after this interval of time is generally confined to a solitary metastatic lesion.

Malignant tumors of the testicle are a local disease for a certain period of time. If the diagnosis is made and orchiectomy performed during this period, the hope of cure is excellent. Therefore, after a diagnosis of tumor is established, immediate excision is mandatory.

An interesting observation of the 15 instances of cryptorchidism is that in 4 cases (26 per cent) the normal mate was the seat of the tumor. This finding tends to refute the opinion that the undescended testicle develops malignancy more often than the normally placed testis. It was also noted that in 4 cases where an orchiopexy had been performed with no clinical evidence of tumor at the time of surgery, the patients later developed malignant tumors. This raises the question as to the validity of the argument of carrying out orchiopexy in the undescended testicle as a prophylatic measure to avoid malignancy.

The treatment of testicular tumors depends largely on their type, and I would like to stress the importance of acquiring serial histologic sections because of the multiplicity of cellular structure sometimes encountered in various parts of the same specimen. Recently, I had a patient on whom *one* section of the tumor was pure seminoma, while another section of the same tumor contained seminoma and embryonal carcinoma. The latter finding not only changed the prognosis but altered the mode of therapy.

Preoperative radiation in tumors of the testicle should be condemned for the following reasons: 1) Valuable time may be lost before the tumor is removed and

2) Radiation destroys the original architecture of the tumor, complicating an accurate microscopic diagnosis. 3) Benign tumors inadvertently are radiated. 4) Some tumors are radiosensitive and others are radioresistant.

The therapeutic value of postoperative radiation has been shown in greatly increased survival rates, but all testicular tumors are not equally radiosensitive. The adult type of teratoma does not respond to radiation, even though 65 per cent of these tumors in this study received postoperative roentgen therapy. A lethal tumor dose of radiation for a seminoma consists of about 1500–2000r, an amount which can be delivered without injury to surrounding structures. If there is an admixture of other tumor types within the seminoma, radiation should always be given in larger doses. Embryonal carcinoma and teratocarcinoma are much more radioresistant and require a tumor dose of 5000–7000r. This amount of radiation frequently distresses the patient and may cause late radiation injuries. Choriocarcinomas are radioresistant and spread so early through the veins that radiation of lymph channels has proven of little value.

Owing to the lack of subjective symptoms, patients are reluctant to obtain medical advice and often the attending physician procrastinates unnecessarily before surgical extirpation of the testicular tumor. The only hope for improving results of treatment in testicular tumors is by educating the laity and the medical profession to become more cancer conscious.

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THE EVALUATION OF HORMONAL THERAPY IN CRYPTORCHIDISM

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After 25 years of prescribing and using hormones for the treatment of cryptorchidism, it is time that we arrive at some definite evaluation of the therapy. Hasty and incomplete clinical observations, coupled with too little regard for research, have given the pediatrician who first views these patients a misconception of the actual facts. Webster claimed that the use of hormone caused [illegible] per cent of cryptorchids to migrate to the scrotum, while Lowsley claims [illegible] per cent. The literature contains many reports of percentages between these two extremes. The age at which hormonal therapy should be given has also been a point of contention. Some advise its administration from the second year on through puberty; others support hormonal therapy in full-grown adults. The type of hormone used, the length of time of its administration, and the amount given vary in different clinics. The preceding points of contention should now be clarified and a regime of treatment be determined which is rational and will give constant results in the hands of all physicians.

There is no doubt that the chorionic hormone, the so-called anterior pituitary-like substance derived from pregnancy urine, is a factor in the mobility of the undescended testis. The experimental work of Engle, Moore, DeJongh, Bourg, Deming and others conclusively demonstrates this contention. Womack and Koch found the greatest amount of this hormone in the foetus, that it was practically absent in boys up to 10 years of age and that it was present in large amounts during adolescence and up to 40 years of age, after which it gradually declined in amount. The testis usually descends into the scrotum between the seventh and ninth month *in utero*. It is estimated that 1 per cent of the testes is undescended at birth. There is no doubt that some descend at puberty. After the adolescent period is past one would not expect the cryptorchid to descend and this has been our clinical experience. The biological and clinical pictures support the action of this hormone.

Before birth and at birth, under normal conditions, both testes have an equal opportunity to descend into the scrotum. Clinically, unilateral cryptorchids far exceed the bilateral lesion. If one testis descends and one remains a cryptorchid there must be some factor other than hormonal which influences the retention of the testis along the canal, such as abnormal attachment of the gubernaculum, deformity of the organ, hernia, hydrocele, ectopia, or malformation. There may be a congenital absence of the organ. If both testes remain cryptorchids then one might hypotheecate that, with normal gonads and in the absence of obstruction, there may have been *in utero* a subnormal amount of the hormone present at the opportune time for descent. Assuming this condition, an ideal situation would be present for a successful descent after hormonal therapy.

Read at annual meeting, American Association of Genito-Urinary Surgeons, [illegible] Pa., May 18, 1951

The motive force which causes a descent of the testes is not present within the testis, nor is the gubernaculum responsible for its descent, for the latter only guides the direction of movement. Thompson and Heckel and Moore and Tapper have referred to the absence or near absence of the cremaster muscle in the cryptorchid. Hart has clearly shown in his experimental work on the marsupials that the cremaster muscle exerts a milking action on the testes and that the gubernaculum acts only as a guide. Further evidence is demonstrated in the author's work on the rhesus monkey. This animal is born with descended testes which, after four or five days, ascend into the abdomen or to the internal inguinal ring until adolescence, the sixth year, when they naturally descend into the scrotum.

The author's experimental work embraces a histological study and comparison of tissues before and after injection of gonadotropic hormone in pre-adolescent macaque monkeys. A section of the inguinal canal and cord were taken on one side as a control; and when, after a month's hormonal treatment, the remaining testicle had descended into the scrotum it was removed for microscopic study. The descended testes showed grossly a 50 per cent increase in size with histological evidence of an increase in the diameter of the tubules and some increase in interstitial tissue. The tubules of the epididymis had become larger at the expense of the intertubular tissue. The epithelial cells lining the tubules were taller and appeared more active but there was no gametogenetic activity. The vas had enlarged two or three times and had become elongated and the vascularity of the whole cord was greatly accentuated. There was an increase in the size of the lymph spaces with a deposit of fatty tissue, and the cremaster muscle fibers were twice the size of the control. Examination of the scrotum showed the dartos muscle to be greatly increased in size with large lymph spaces and increased vascularity but there was no change in the skin. The effect of the gonadotropic factor is not only to widen the inguinal canal but also to increase the size of all the cord structures and the scrotum except the skin and to cause the testes to descend into the scrotum without the development of hernia. The same conditions can be produced by hormonal therapy in the human male child as have been produced in the pre-adolescent monkey unless mechanical obstructive factors or structural abnormalities are present. These artificially produced tissue changes are comparable to those normally seen in the adolescent child, when the gonadotropic hormone is present in the greatest amount. If we can apply hormonal therapy in the child to cause the cryptorchids to descend into the scrotum without the development of sexual maturity we will have accomplished the desired result.

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intended its transplantation fourteen years earlier. We have been unsuccessful in treating adults by hormonal means alone.

CASES FOR HORMONAL TREATMENT

It is quite obvious that not all cases of cryptorchidism are suitable for hormonal treatment. Contra-indications for hormonal therapy are found in boys with an ectopic testis or an accompanying large hydrocele or hernia. The most favorable conditions exist when the testis lies in the inguinal canal and cannot be forced into the scrotum or when there is a bilateral cryptorchidism whether or not the testes can be palpated. There is always a reason why testes do not descend into the scrotum. If both testes remain as cryptorchids one can hypothecate that the reason for failure to descend was a subnormal amount of the hormone at the eighth and ninth month *in utero* and can expect that these cases will respond to hormone therapy. One should rarely expect to be successful in the hormonal treatment of unilateral cryptorchidism because both testes have been subject to equal effects of the hormone *in utero*. The physician should exercise greater diligence in the examination of these conditions. One rarely sees a fully developed scrotum in a child with an intra-abdominal testis and the scrotum is never developed on the side where there is a congenital absence of the testis, so that there are, theoretically, only a few cases of cryptorchidism where a successful descent of the testes can be produced by hormonal therapy alone.

TYPE OF HORMONE

The hormone known as Follutin-S is the hormone used in our clinic. Usually 250 international units are given intramuscularly 3 times a week for 4 weeks for a total of 3,000 units. This amount is sufficient to produce an artificial adolescence *with a slight edema of the foreskin and scrotum* and the descent of the testis will follow in this period if it is to come down at adolescence. In other words, a false adolescence is produced. It will not cause much actual growth of the phallus or of pubic hair. The administration of lesser amounts over a longer period of time seems injudicious and the giving of more units unnecessary. Recently in the *Journal of the American Medical Association* the question was asked and answered as to hormonal therapy for the undescended testis. Advice was advanced that 30,000 units should be given over a six to eight week period in children 11 to 14 years of age. We can not subscribe to this advice. If too much hormone over too long a period is given there are adverse reactions which must be kept in mind, such as precocious sex development and closure of some of the epiphyseal bone centers, which prevents the full development of long bones. One must be fully cognizant of the harmful effects resulting from the use of the gonadotropic hormone as well as its value.

Androgenic hormone has been advocated by several authors as superior to the anterior pituitary-like hormone in producing a descent of the cryptorchid. In the male puppy, androgen causes an aspermia and loss of gametogenetic products. Heckel has reminded us of the diminished spermatogenesis in the human after male hormone therapy. If spermatogenesis is a factor to be desired at this should not be given for cases of cryptorchidism. We use androgen if the testes do not develop after they have been surgically transplanted to the scrotum.

It is quite evident that one can expect a full descent of the cryptorchids by the use of chorionic gonadotropic hormone alone in only a few cases, probably 5 per cent or less. Its greatest usefulness is as an adjunct to a surgical orchidopexy because it elongates all the cord structures, including the vas and vessels, and prepares the scrotum for reception of the testicle. A regular course of hormonal therapy is given preoperatively in selected cases and the surgical procedure done immediately. The technique of the operation is greatly facilitated and even in the most difficult cases sufficient cord length can be obtained by transplanting the testis beneath the deep epigastric vessels. We have never had to perform an orchidectomy after adequate preoperative hormonal therapy.

Of 189 cases of cryptorchidism, descent of the testis took place with hormonal therapy alone in ten cases, or 5 per cent. Of the 201 surgically treated undescended testes, agenesis of one testis was present in 9. Orchiectomy was required in 12 cases because of short vessels or a deformed organ, but only one of these patients had been subjected to preoperative hormonal therapy and that one inadequately. The main use of chorionic gonadotropic hormone is as an adjunct to surgery.

SUMMARY

The hormone containing chorionic anterior pituitary-like substance is of particular value in the treatment of cryptorchidism.

Follutin-S, 250 international units, given intramuscularly 3 times a week for a total of 3,000 units is sufficient.

Optimum age is the fifth year.

Hormonal therapy will cause the full descent of the cryptorchid in about 5 per cent of the cases.

Its greatest value is (as) an adjunct to surgery.

Surgical orchiectomy has never been necessary following adequate hormonal therapy.

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SURGICAL TREATMENT OF CRYPTORCHIDISM

JOSEPH H. KIEFER

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The need for surgical correction of persistent cryptorchidism is now generally accepted. The failure of the retained testis to develop fully was described by John Hunter more than 150 years ago. The excellent and thorough work of Carl Moore proved the need of the testis for an environment at a temperature below that of the body normal.

While the failure to mature is the chief reason for bringing down the cryptorchid testis, there are others of importance. The possibility of malignant degeneration is of such magnitude as to demand consideration. Our own experience has been such that we feel that this factor alone warrants orchiopexy, even in the adult. The cosmetic factor, although not medically important, should not be disregarded.

Endocrine therapy of cryptorchidism has now assumed a different role from that assigned to it when it was introduced. It is now more often used as a test or as an adjunct to surgery rather than as a sole mode of treatment. We use endocrine injections before surgery in most prepubertal cases. This establishes whether or not the testis can descend into the scrotum with endocrine stimulation alone. If it can, and there is no separate indication for surgery such as associated hernia, the child is allowed to wait until puberty when the normal endocrine stimulus operating at that time can be expected to effect descent. If endocrine injections are ineffective, surgery is then done before puberty.

Most urologists make an effort to bring the testis down into the scrotum before pubertal changes begin to appear. There are some, a minority, who wait for a year or two after pubertal changes become apparent. We have felt that the testis has the best chance of responding to the endocrine stimuli of puberty if it is already in the scrotum at that time.

The surgical principles underlying the operation of orchiopexy are now well established. The desired result is to have the testis, with the spermatic vessels and the vas deferens intact, in the bottom or midportion of the scrotum.

The testis as well as its nutrient vessels and the vas deferens must be completely liberated. Fixation of the freed testis in the scrotum is considered necessary by most urologists today. It is relative to the method of fixation that most differences of opinion have arisen and different techniques devised.

The following is a brief description of the surgical technique we now use, with brief comments about alternative procedures that have been tried. Our technique is shown in figures 1, 2, 3, 4 and 5.

The usual inguinal incision is used, if necessary extended up beyond the anterior superior spine. The inguinal canal is opened and the testis, if there, is freed up. The gubernacular structures, if present, are dissected to their points of attachment and divided.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Skytop, Pa., May 18, 1951

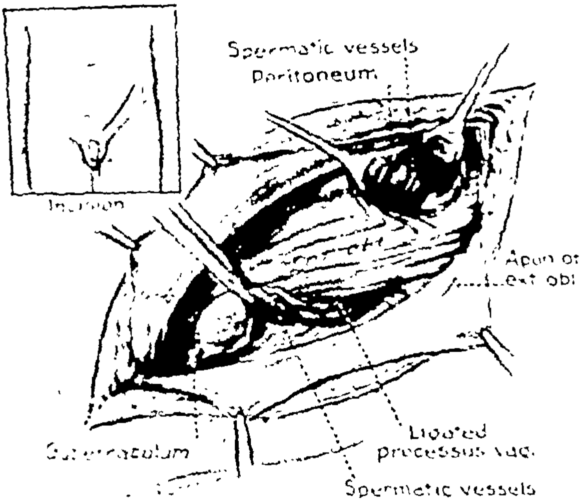
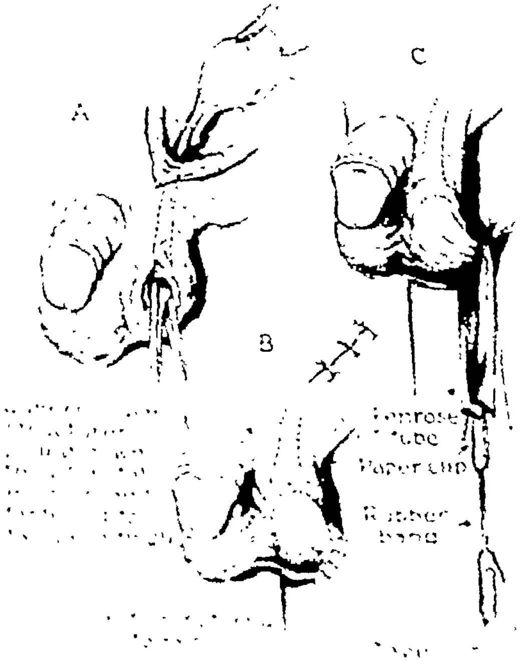


Fig. 1. Muscle splitting opening above inguinal canal. This is helpful in freeing spermatic vessels high in abdomen. Peritoneal cavity can also be opened and explored through this.



cases in which the testis is situated high in the inguinal canal or in the abdomen, the vas and epididymis may extend well down into the inguinal canal and they turn back to join the testis and this loop may easily be injured.

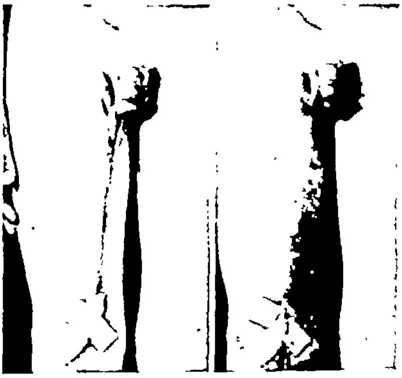


FIG. 3. After application of traction for many weeks

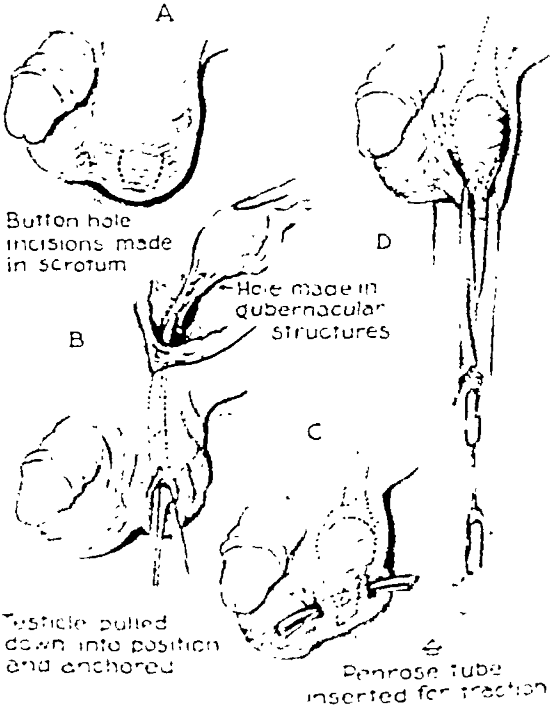

A
Button hole incisions made in scrotum
Hole made in gubernacular structures
B
D
C
Testicle pulled down into position and anchored
Penrose tube inserted for traction

FIG. 4. Method of applying traction through a button hole made through gubernacular structures.

If the testis is not in the inguinal canal, abdominal pressure by the surgeon will often help to extrude it through the internal ring. If the testis is still not located, the processus vaginalis, if present, is opened and the finger inserted [illegible] the peritoneal cavity. The testis may be felt in any direction, but commonly below or lateral to the internal ring. It is usually possible to bring it through the internal ring without great difficulty. If the testis is fixed up high in the abdomen, it is better to approach and free it intra-abdominally through a separate muscle splitting opening higher up.

One of the most important parts of the operation is the complete freeing of the cord structures from the overlying peritoneum of the processus vaginalis. The peritoneum is divided just proximal to the testis and removed completely. In cryptorchidism this peritoneum is much more adherent to the cord than it is in the ordinary inguinal hernia. The very tight adhesion between the peritoneum and the cord structures is an important factor in preventing complete descent. Injection of liquid by needle just under the peritoneum is a useful maneuver to develop the proper cleavage plane.

All connective tissue strands joining the peritoneum and the cord elements must be thoroughly and completely divided. Likewise, all remnants of the internal and external spermatic fascias as well as the cremaster muscle must be re-

Fig. 5. Button hole traction arrangement

vessels helps to locate them. From this point they are freed completely from any peritoneal or other adhesions both down to the inguinal ring and up to a point above the pelvic brim, thus allowing the maximum extension.

If the testis cannot be located in the groin or near the internal ring, this type of incision allows one to do an intraperitoneal exploration. On removing the retractors, the muscles fall back to their normal positions immediately and one or two sutures are enough to make a sound closure. This maneuver is much more satisfactory than cutting the lateral fibers of the conjoined tendon. It gives exposure where needed and the closure is better.

Lack of length of the vas deferens is seldom a cause of trouble or of failure to bring the testis all the way down into the scrotum. As mentioned above, in many of these cases the epididymis is not attached to the testis and mere rotation of the testis allows sufficient extra length in the vas. In those cases where the vas is a little short, it was suggested by Frangenheim in 1920 that the testis and the spermatic vessels be brought underneath the epigastric vessels. This is done without difficulty but we have not found it to give much additional length, *seldom more than 5 or 10 mm. It is not desirable to bring* the cord structures under the epigastric vessels. If for any reason whatsoever, later surgery were done in this area, the exposed epigastric vessels might easily be injured and lead to troublesome hemorrhage. If they are in the way, it is much better to doubly ligate and sever the vessels rather than slip the testis underneath them and leave them intact in an abnormal location. We have not used the procedure of making a new artificial opening through the muscles medial to the epigastric vessels, as suggested by Fruin. By this method the cord emerges at about the same point as it does when the epigastric vessels are ligated.

The Ferguson type of inguinal canal repair is used because it brings the cord out through all the layers at the site of the external ring.

After the testis and its vessels have been completely freed from the surrounding structures and sufficient length obtained so that the testis may be brought well down in the scrotum, there is still the question of fixation. A few men have expressed the opinion that if the testis and cord have been adequately freed up, no fixation will be required. Those of this opinion are definitely in the minority. Most urologists believe that fixation is desirable. We have felt that fixation of one form or another is useful in practically every case.

The scrotum is nearly always small and underdeveloped and despite vigorous stretching to form a pouch there is a very strong tendency for the scrotal tissues to recontract, and force the testis back up to the neck of the scrotum or even to the external ring. It has been stated that complete sectioning of the cremasteric and other fascias and placing the testicle through the opening so made would prevent retraction. There will still remain the dartos fibers in the very skin itself whose action will tend to push the testis back up. Also, the cord structures will tend to contract and the scarring of the inguinal structures incident to healing can in itself cause retraction.

Methods of fixation advocated have been numerous and varied. The first recorded orchiopexy by Rosenmerkel in 1820 was described as including [illegible] to the bottom of the scrotum with a suture. Suture of the testis to the bottom of the scrotum continued to be most popular, but apparently then, as now, proved to be inadequate. Procedures to fix the testicle in the scrotum by closure of the scrotal neck were next tried. Bevan's method was based on this idea. The procedure fell into disuse because of its ineffectiveness, particularly if there was still any tension on the cord structures. Other efforts to fix the testicle included transplantation both under the skin of the thigh or to the scrotal sac on the opposite side. Fixation by suture in other locations such as in the perineum or to the pubic bone was also tried.

When it was found that the retracting testis would pull the scrotum with it, the next step was to attempt to hold down both the scrotum and the attached testis. Sutures were placed through the bottom of the scrotum and through the skin of the thigh. Elastic or other materials were placed through the scrotum and attached to wire frames or to the adjacent or opposite thigh.

Suture traction was not completely effective because the tension could be maintained for only a limited period. Sutures cut through within a short time and as the tendency to retraction usually continued beyond this time, the method often failed.

The next step was to make a semi-permanent attachment of the testis to the thigh through skin incisions. Although Keetley first advocated this principle, Torek popularized it in this country, using sutures through the body of the testis itself. Torek's method had a serious disadvantage in that if wound infection occurred, the tunica of the testis might be so badly damaged that the parenchyma would be extruded and lost.

Keetley had advocated fixation to the thigh not of the testis itself but of the fascial structures attached to it. This obviated any damage to the testis by the sutures and simplified the later separation from the thigh. This method has since been redescribed by many authors. It is the method I was taught by Dr. Charles Morgan McKenna and I still use it in most cases. It provides excellent fixation, is easily detached, and I know of no serious objection to its use. More elaborate methods of fixation such as raising fascial strips or flaps have never become lar structures after they have been attached to the deep fascia of the thigh. This has been tried in a small number of patients. It has been effective in some of them in loosening the tissue of the spermatic cord and bringing the testis down to lie more loosely and naturally in the scrotum. See figure 2.

The traction is easily applied using a small rubber tissue drain wrapped around the isthmus and connecting to a rubber band which in turn is stretched down to an adhesive plaster anchor on the inner side of the thigh just about the knee. The tension is easily adjusted either by changing the position of the anchor or by adding or subtracting small paper clips which are used as connecting links.

If the tension is applied mildly at first and gradually increased, most boys can wear this with no discomfort and no disability or restriction of activity. The patient must be careful to keep the skin in the area clean and dry to prevent excoriation, especially in the warm weather when there is much perspiration. The device is easily applied and removed by the patient himself and he can take it off any time it becomes uncomfortable.

The process is necessarily slow and the patient must usually wear the device for several weeks before any effect becomes apparent. Some will just not bother with it, but there is no question but that the continued traction can draw the testis down farther. See figure 3.

The advantage of this method is that the tension may be continued indefinitely and in increasing amounts if desired, time not being limited by the period during which one or more sutures will cut through the tissues. Of course, traction is not started until the anastomosis between the testis and thigh is well healed so that separation of the anastomosis will not occur.

When the testis has either reached a desired position or it is felt that no further improvement is to be expected with reasonable amounts of tension, a trial period without tension will then indicate whether retraction is going to occur.

In a couple of cases, an attempt was made to provide a point for traction by making a button hole through the tissue of the gubernaculum or of the reflected tunica vaginalis. A skin tunnel was then made through this opening by making two small scrotal incisions and sewing them together through the loop. It was possible to get some traction on the testis by this method, but in neither case was the attempt clinically successful. In one case the skin bridge was too small and the tension soon cut through, even with a small strip of flat rubber tissue to even pressure. In the other, the patient did not cooperate. See figures 4 and 5.

The number of cases where such measures are considered is small; the great majority require only temporary suture fixation or gubernacular fixation to the thigh and later detachment.

Our experience with secondary operations to bring down the testis which could not be properly located on the first operation has been small but disappointing. We have come to the conclusion that the first operation is the best time to gain whatever mobilization of the testis it is possible to obtain. The second operation has always been attended with much more difficulty from adhesions; anatomical landmarks are lost and the testis has been no more willing to come down on the second operation than it was on the first.

Despite Bevan's confident assertion that the spermatic vessels could be divided without serious consequence, the experience of many urologists has been contrary and atrophy of the testis has been the eventual result.

There will occasionally arise the question as to whether orchiectomy should be done. Despite every effort there are some cases in which the testis cannot be brought down far enough to be placed in the scrotum at all, much less to be fastened to the thigh. Also, some of these testes will be very hypoplastic. The answer to the question as to whether a testis should be removed will depend on three factors: 1) the site to which it is possible to bring the testis; 2) the apparent worth of the testis from a functional standpoint; and 3) the state of the other testis.

If the testis on the opposite side is apparently normal, it would be poor policy to leave a hypoplastic testis in the groin or in the abdomen. If the involved testis is of nearly normal size, one would be more reluctant to sacrifice it even though the other testis were normal. It is a debatable point whether such a testis might best be left in the region of the external ring outside of the fascia but not immediately over the pubic bone. In such a position it would be amenable to regular examination and any change in its size would be readily apparent. With a normal testis on the other side, one should never replace a cryptorchid testis in the abdomen or leave it in the inguinal canal. The possibility of malignant degeneration outweighs the expected benefit from such a procedure.

Where the testis on the other side is subnormal or of unknown value, one will naturally extend his efforts to preserve even a hypoplastic testis. Even so, one should hesitate to replace such a testis in the abdomen, preferring to leave it in the subcutaneous inguinal space where it would be amenable to examination. The excellent results of replacement androgen therapy make one less hesitant to remove an abnormal testis but, where one can do so without extraordinary risk, one should leave the patient with a functioning testis so he will not have to rely on constant replacement medication.

SUMMARY

Surgery is the accepted treatment for cryptorchidism which does not respond to a trial of endocrine therapy.

The basic principle of surgical treatment is complete freeing of the cord structures from all adhesion to adjacent structures.

Fixation of the testis in the scrotum is desirable and necessary in nearly all instances to insure against retraction from the scrotum.

It is occasionally possible to continue traction indefinitely after surgery by use of an elastic band.

Orchiectomy is only rarely indicated.

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MASSIVE HEMANGIOMA OF THE SCROTUM

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Excellent reviews of the literature relative to hemangioma of the scrotum with reports of individual cases have been presented by Gibson[1] and Winslow[2] and others. It is the purpose of this paper to present an additional case, and to record the first such case to our knowledge that has been studied by arteriography.

G. S., a 16 year old boy, was referred for consultation because of gradual increase in the size of the scrotum, associated with the sensation of weight, which the lad said was "getting heavier by the week." The mass had been present for approximately 8 months, was not painful, and its large size could not be concealed by any clothes the boy normally wore. There were no constitutional symptoms. The boy's past history and family history were irrelevant.

Examination of the scrotum by inspection revealed a mass slightly larger on the left than on the right. The skin over the mass had a bluish tinge and it appeared as though there were numerous subcutaneous venous channels. The mass extended to the upper edge of the scrotal skin but not into the inguinal areas.

On palpation, the mass was nontender. There was thickening of the skin with associated thickening of the subcutaneous tissues. The mass felt like the "bag of worms" commonly referred to in describing varicoceles. There was, however, no involvement of the spermatic cord on either side. Both testicles were of normal size and shape, and lay anterior to the mass, which measured 48 cm. in circumference (fig. 1). Auscultation revealed a definite bruit, more marked on the left than on the right.

Tissue for biopsy was removed. The pathological report was capillary and cavernous hemangioma involving skin and subcutaneous tissue (fig. 2).

Arteriograms were obtained by injection of the aorta with sodium iodide which revealed a portion of the blood supply to be the superficial and deep external pudendal branches of the femoral artery, as well as a large vessel descending in the pelvis, most likely the terminal branches of the internal pudendals (fig. 3). Obliteration of the external pudendals and posterior scrotal branches of the internal pudendals was accomplished by ligation bilaterally, this portion of the operative procedure being carried out by Dr. Henry Garrigues of Seattle. The point of ligation and blood supply to the normal scrotum is shown in figure 4.

Following obliteration of the major portion of the blood supply, arteriograms were obtained which are shown in figure 5. The mass decreased in size markedly, and on examination three months later, its circumference measured only 20 cm. [illegible] of the mass was accomplished after first delivering and isolating the

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[1] Gibson, T. E.: Urol. and Cut. Rev., 41: 817-818, 1937.
[2] Winslow, N.: Arch. Surg., 13: 820-823, 1926.

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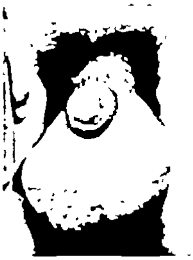


FIG. 1

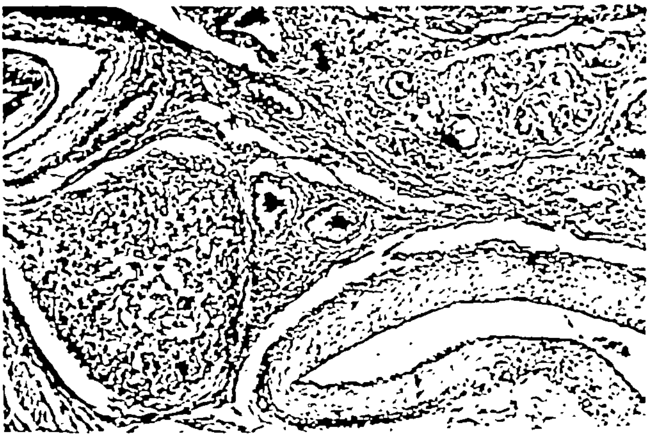


FIG. 2

FIG. 3

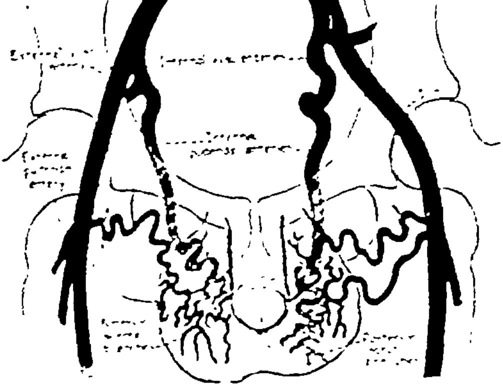


Fig. 4

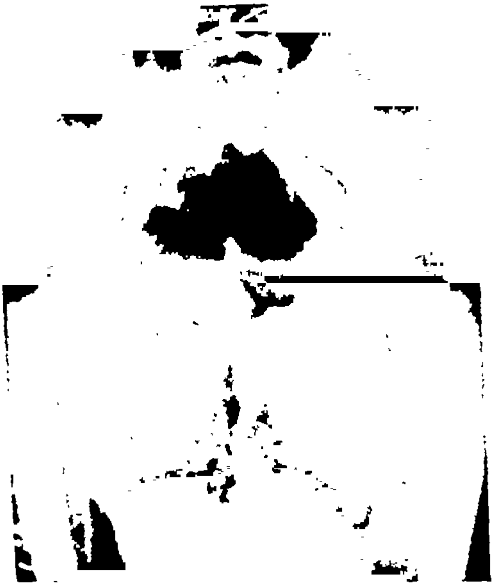
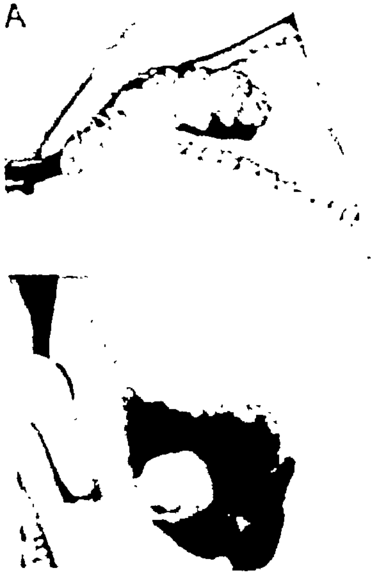


Fig. 5



[illegible]

testicles to the abdomen through bilateral inguinal incisions. Inguinal nodes removed at this stage showed no evidence of disease. With the testicles out of the way, it was possible to do a radical resection of all visible hemangioma, leaving a cuff of normal scrotum. Upon completion of the procedure, the testicles were returned to their normal position and sutured to the lateral wall to prevent torsion. The inguinal and scrotal wounds were closed in the usual manner with drainage (fig. 6, *A*). The removed operative specimen weighed 827 gm. Postoperative course was uneventful. The patient was discharged from the hospital on the eighth postoperative day. He was last seen 10 months after operation. There is no evidence of recurrence (fig. 6,*B*).

SUMMARY AND CONCLUSIONS

A patient with massive hemangioma of the scrotum is presented. Preoperative workup consisted of removal of tissue for biopsy, arteriogram to determine the blood supply of the lesion, followed by surgical interruption of the major portion of the blood supply. Protection of the testicles was accomplished by their complete removal from the scrotal integument during excision of the hemangioma.*

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* Arteriograms were taken by Dr. O. A. Nelson of Seattle.

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PRIAPISM: AN UNUSUAL COMPLICATION OF TETANUS ANTITOXIN INJECTION

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When one attempts to look up the subject of priapism in the literature, one is surprised at the scarcity of articles. Hinman, in 1914, reviewed the literature and reported 170 cases. As of 1947, there have been reported slightly over 200 cases.

Priapism is a pathologic condition characterized by prolonged and persistent erection of the penis unaccompanied by sexual desire and usually painful. It is usually, if not always, a manifestation of some other disease. Recently, a case of priapism was encountered following an injection of 1500 units of tetanus antitoxin and for which no other cause could be elicited. The rarity of this etiological factor warrants this report.

CASE REPORT

P. C., a white laborer of 33 years, stepped on a nail which penetrated his right foot on May 17, 1950, while at work. He was first seen for this injury on the next day and 1500 units of tetanus antitoxin were given after a negative skin test. There was a small puncture wound on the sole of the right foot without any tenderness or redness about it. This was treated with an antiseptic and dressed.

On May 20, 1950, the patient returned to the office complaining of redness and soreness about the sites of injection of the tetanus antitoxin. He was given an antihistaminic, histadyl, 50 mg. t.i.d. with some relief of symptoms but returned May 25 complaining of a persistent, painful erection of the penis which developed the preceding day, 1 week following the tetanus antitoxin injection.

The patient was given an injection of 5 minims of adrenalin, codeine gr. $\frac{1}{2}$ every 4 hours as needed for the pain and advised to apply hot compresses. He was able to void although only in small quantities. Because of the persistence of erection, severe pain and approaching retention of urine, he was hospitalized on May 27, 1950.

Past history was essentially negative especially for venereal and inflammatory diseases. The patient never had any infection of the urogenital tract. In 1939, he received tetanus antitoxin, followed by hives which lasted several days.

On physical examination the penis was erect, firm, tender and painful especially on the slightest motion so that it was necessary to support it with compresses. The skin of the penis was red but not edematous. The prostate gland [illegible] within normal limits and the scrotal contents were essentially [illegible]. The puncture wound on the sole of the right foot was healed [illegible] redness or swelling at the sites of injection of the tetanus [illegible]. [illegible] temperature [illegible], pulse 100 and respirations 22. Blood pressure [illegible].

[illegible] The blood count showed 4,380,000 red cells and 96 per cent hemoglobin; 17,650 white blood cells with 71 per cent segmented forms, 8 per cent stabs, 19 per cent lymphocytes and 2 per cent monocytes. No immature white blood cells were found and the red blood cells appeared normal. Urinalysis revealed clear, straw colored urine; acid reaction; specific gravity 1008; negative sugar and albumin. Microscopically, there were 3-8 white blood cells per high power field.

Various treatments and medication were given for the relief of pain and reduction of the priapsim. First, pantopon gr. ⅓ every 4 hours was given as needed and a Foley catheter inserted into the bladder. Then 5 minims adrenalin every 10 minutes for 6 doses was administered. The patient was anesthetized for 20 minutes with intravenous pentothal sodium and then 20 cc of 4 per cent procaine were instilled into the bladder. He was then placed on benadryl 50 mg. 4 times daily and hot wet compresses were applied to the penis. None of these procedures produced any appreciable change in the priapism.

On May 29, 1950, because of the persistence of the condition, he was given 5 mg. of 1 per cent pontocaine intraspinally. Following this, the penis could be moved more freely but still remained erect and narcotics were still required for the pain. The spinal fluid showed 128 red blood cells per cu.mm. and 1 poly per cu.mm.; sugar 74 mg/100 cc; total protein 74 mg/100 cc. Wassermann tests on blood and spinal fluid were negative. On June 1, 1950, the Foley catheter was removed and the patient was able to void satisfactorily. A neurological consultation on June 6, 1950 reported the neurological examination essentially negative. There were no signs or symptoms to suggest spinal cord root or nerve disease.

Because of the failure of the preceding measures to cause any change in the condition of the penis, on June 7, 1950, two weeks after the onset of priapism, a large bore needle, 18 gauge, was inserted into the right corpus cavernosum near the base of the penis under novocaine anesthesia and some dark fluid blood was aspirated. A smaller gauge needle was inserted into the left corpus cavernosum just below the coronal sulcus and 1000 cc of normal saline was allowed to flow through the small needle, escaping through the larger one. The fluid contained dark blood and dripped at the rate the fluid entered the small needle. In this way, the cavernous sinuses were irrigated. During this procedure, a definite change could be seen taking place in the penis. It began to soften and the skin which had been tight became loose. There was definite relaxation of the penis at the base and it could be moved more easily without pain. Penicillin, 400,000 units, was administered daily.

On June 8, 1950 the penis was still erect but softer and less painful. Another irrigation of the corpora was done as previously. A third irrigation was performed on June 12, 1950. Two days later, the skin of the penis was loose and appeared normal. The penis could be manipulated in all directions without pain although it was smaller and somewhat firmer than previously. The patient was discharged from the hospital June 20, 1950, twenty-seven days after the onset of the priapism. On follow-up 1 month later, the penis had returned to normal with no residual impairments. At the end of 6 weeks, the patient had [illegible] erections and function. The prostatic smears showed active normal sperm and 5-8 white blood cells per low power field. Nine months later, there were no residuals as a result of the prolonged priapism.

DISCUSSION

Priapism may be considered to be of nervous or mechanical origin. The former is not as common as the latter and is due to prolonged spasm of the ischiocavernosus muscles or to complex nerve stimuli. These are exemplified by spinal cord lesions, multiple sclerosis, syphilis and poisoning by aphrodisiacs. Leukemia, sickle cell anemia and tumors in the corpora or in the pelvic venous plexus are mechanical causes of priapism. It has also been reported following the administration of 100 mg. of testosterone propionate in divided doses over a period of 7 days.

Treatment of priapism may be divided into conservative and operative measures. Sedation and warm wet compresses are recommended if no changes have taken place in the blood in the corpora cavernosum. This may be tried for a period of at least 2 weeks as long as there is no evidence of gangrene. If the latter is present, immediate incision and evacuation are indicated. If conservative treatment is of no avail, aspiration of the corpora cavernosum and irrigation with saline or citrate solution, as advocated by McKay and Colston in 1929, is the procedure of choice. The condition may recur and the procedure may have to be repeated three times before a cure is obtained. However, if this is not successful, incision and drainage under pentothal or general anesthesia are necessary. The functional result is not as good because of the resultant scarring. Penicillin intramuscularly and sulfa locally are also used.

SUMMARY

A case of priapism is reported following tetanus antitoxin injection. This is considered as a complication since no other etiological factor could be found in this particular case.

The treatment was at first conservative using warm wet compresses and sedation. Other conservative measures were tried for two weeks as long as there was no evidence of gangrene. However, aspiration and irrigation of the corpora cavernosum brought about definite improvement which was noticeable during the procedure. Progressive improvement with reduction in size of the penis was observed with each treatment.

It seems reasonable to assume that the injection of the tetanus antitoxin was the competent producing cause for the persistent priapism and was accepted as such by the compensation court.

[illegible] St., Poughkeepsie, N. Y.

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CONSERVATIVE AMPUTATION OF THE PENIS FOR CARCINOMA

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The purpose of this paper is to describe a simple but adequate procedure for conservative amputation of the penis which the writer has employed with few modifications in about 150 cases. The operation is based on the fact that penile carcinomas, like other epidermoid cancers, metastasize by embolism and, therefore, all of the primary growth can be removed when amputation is performed 1.0 to 1.5 cm. proximal to any visible or palpable evidence of disease. Enough of the penis thus is conserved to direct the urinary stream and occasionally to perform coitus.

Since the operation is performed quickly without shock, no special general preparation of the patient is required. Cleansing the growth with soaks in warm medicated solutions, formerly the principal preoperative measure, is now but a supplement to use of chemotherapy and antibiotics. The amputation can, therefore, be done soon after the diagnosis has been established by microscopic examination. When the biopsy is performed, one should take the opportunity of demonstrating that the penis is involved with tumor because occasionally only the prepuce is affected and no more than a circumcision may be needed.

A low spinal anesthesia is used. After the usual skin preparation, a tourniquet is placed about the base of the penis. A hand towel is then folded over the infected ulcerated tumor. The edge of this towel may be carefully fixed with clips about 1.5 cm. proximal to the growth to indicate the line of incision (fig. 1, A). With a large scalpel, a guillotine amputation is quickly performed and the foul growth, still securely enclosed in the sterile towel, is carried from the operating room. The subcutaneous dorsal vessels now should be ligated with a suture ligature but usually no other vessels need attention at this time.

With the penis clearly exposed in cross section (fig. 1, *B*) one should search for residual tumor. If present, it is pearly gray or pale yellow in color and is most likely to be in lymphatics accompanying the larger veins. I have never made such a discovery and it must be rare because local recurrences are so uncommon. It would, however, call for amputation at a higher level.

The corpus cavernosum urethra is now dissected from the corpora cavernosa penis for a distance of 1.0 cm. (fig. 1, *B*). At the proximal end of this separation, a double ligature of No. 1 chromic catgut on a straight needle is passed through the septum between the corpora cavernosa penis. When the needle has been cut from this doubled suture, a single suture can be tied around each corpus cavernosum (fig. 1, *C* and 2, *A*). The tourniquet is now removed. A few insignificant vessels may require clamping and ligating but the two urethral arteries which may spurt from their positions at 3 and 9 o'clock respectively in the wall of the corpus cavernosum urethra are temporarily ignored.

Read at annual meeting, American Association of Genito Urinary Surgeons, [illegible] Pa., May 17, 1951.

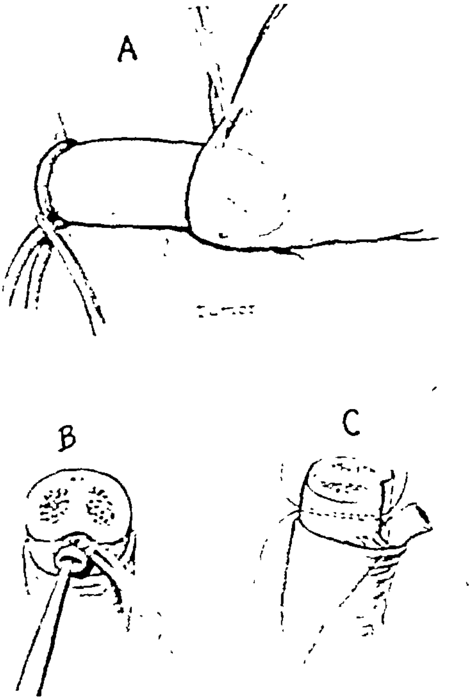
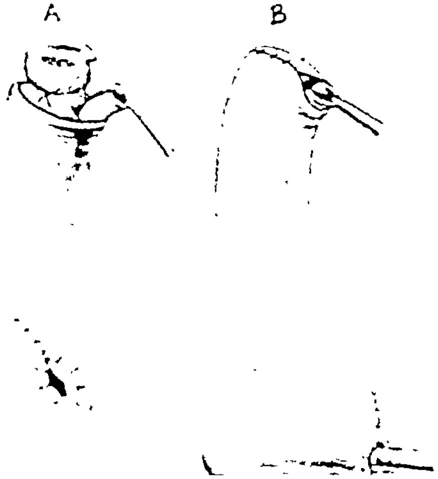


Fig. 1. *A*, with a tourniquet applied to base of penis, a towel is folded over growth and is fastened so that its edge indicates the line of amputation. *B*, penis is seen in cross section after amputation of tumor bearing portion. Dissection of corpus cavernosum urethra is about one half completed. Urethral arteries are located in this structure at 3 and 9 o'clock respectively. *C*, corpus cavernosum urethra has been freed sufficiently and a doubled ligature has been passed through the septum between the corpora cavernosa penis.



A slit nearly 1 cm. long is now made in the dorsal aspect of the corpus cavernosum urethra (fig. 2, *A*) and the entire cut edge of this structure is joined to the cut edge of the skin by interrupted sutures of No. 4 chromic catgut. Some of these sutures stop the bleeding of the urethral arteries (fig. 2, *B* and *C*).

The stump of the corpora cavernosa penis is now covered by joining the remaining skin edges with a continuous suture of plain catgut. As shown in figure 2, *B*, the stump may be covered before the urethra has been sewn to the skin. This does not alter the operation but it is more difficult to first cover the stump and leave just the length of skin needed for apposition to the urethra than it is to first join the edges of these structures and then cover the penis stump with the skin which remains. An indwelling catheter is inserted and is used for about 4 days or until there is no further need for a dressing which might interfere with urination.

These patients are confined to bed only until they recover from the anesthetic. They have little discomfort and there has been no mortality. In but one instance was there a recurrence of tumor in the operative site. A second conservative amputation was performed and this patient now has been free from all evidence of disease for 8 years.

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CONGENITAL ABSENCE OF THE VAS DEFERENS: REPORT OF THREE CASES

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Congenital absence of the vas deferens is among the rare anomalies of the genito-urinary tract in contrast to the more commonly encountered anomalies in other portions of this system. Reports of this condition are appearing with increasing frequency and its instance may be less rare than formerly considered. Several authors have recently published excellent reviews of the literature on absence of the vas deferens. After an extensive search of the literature, Nelson found only 25 cases to which he added three of his own. It is our purpose to present three additional cases of this condition and to discuss the most probable embryological cause.

CASE REPORTS

somewhat redundant with both proximal and distal ends terminating blindly with no connection to the epididymis. This isolated remnant or vestigial vas was the only structure discovered in the cord other than muscle, nerves and blood vessels. Small openings were made in the tunica of both testes and some fluid expressed revealing complete absence of sperm. Biopsy of the testicles later revealed the right to show no evidence of spermatogenesis while the left disclosed some evidence of incomplete spermatogenesis.

Case 2. J. W. R., University of Virginia Hospital No. 219130, a 35 year old white man, was referred for sterility studies. He had been married for 10 years without conception. The patient gave a history of gonorrheal urethritis treated successfully without complications 11 years prior to admission. There was no history of mumps or orchitis. General health had always been excellent. Sexual relationships were said to be entirely satisfactory as were libido and potentia. The patient gave a history of having been examined by several urologists who reported a few immature sperm found at times in the semen specimen. He had had prostatic massages, endocrine preparations and endoscopic attempts to dilate the ejaculatory ducts, all without success or improvement in the semen findings. External genitalia were normal in appearance. The testes were descended and of normal size and consistency. The epididymides could be palpated and they were not unusual in size and without induration. The right vas deferens could be palpated and was not thought to be abnormal. The left vas deferens could not be palpated. The prostate and seminal vesicles were found to be normal on digital examination. Expressed prostatic secretion revealed absence of spermatozoa and only a rare white blood cell per high power field was seen. Several semen analyses revealed azospermia.

Surgical biopsy of the left testicle revealed active spermatogenesis and it was decided that the absence of sperm in the ejaculate was probably on the basis of mechanical obstruction of the vas. Surgical exploration of the scrotum was then advised and performed. On the left the testicle, epididymis, both globus major and minor were entirely normal. There was no vas extending from the globus minor. Careful dissection of the cord up to the inguinal ring on this side revealed no structures except blood vessels and muscles. There was complete absence of the vas deferens. Aspiration of the contents of the epididymis revealed normal active sperm. Exploration of the right scrotal contents revealed again a normal testis and epididymis. The epididymides on both sides did have the appearance of dilatation of the individual tubules. The testicle on the right was entirely normal in size, contour, general appearance and consistency. The vas deferens leaving the globus minor was perhaps slightly smaller than normal and just below the external inguinal ring it had a slightly beaded appearance. The vas was opened above the globus minor and the lumen easily discovered. A small stilet could be threaded down the lumen of the vas into the region of the globus minor. It could be threaded up the lumen to the region of the external ring but not beyond this point. Injection of fluid in the proximal vas under considerable pressure revealed complete obstruction. The operator could not decide whether he dealing with partial atresia of the lumen on this side or secondary atresia from previous inflammation. Aspiration of the globus major on this side again revealed normal active sperm. Because of the presence of active sperm and the hopelessness of establishing any communication with the posterior urethra the writer aspirated the contents of the epididymides and injected them into the cervix of the wife of the patient but to no avail.

Case 3. S. M. G., University of Virginia Hospital No. 148143, a 28 year old white man, had been married 2½ years during which time conception had not occurred. He had always been in good general health. There was no past history of venereal disease, mumps or orchitis. Sexual intercourse was normal in every respect. Physical examination revealed the genitalia to be that of a normal male. Both testes were of average size and consistency and normally descended. The epididymides were easily palpable and considered to be well within the limits of normal. The vas deferens on either side could not be palpated. Rectal examination revealed a prostate gland normal in size and consistency. Expressed prostatic secretion showed an occasional white blood cell per high power field and many lecithin bodies. Urinalysis revealed no abnormal findings. Two masturbated semen specimens were studied. Each showed a volume of approximately 3 cc with no spermatozoa present. A biopsy of the right testis showed tubules with active spermatogenesis and numerous normal sperm within the tubules. Cystoscopic examination showed a normal vesical orifice and bladder. The trigone was well formed and both orifices were in their usual position. The verumontanum was entirely normal in appearance and the ejaculatory ducts were easily visualized in their normal site. The left ejaculatory duct could not be entered. A small catheter was readily passed down the right ejaculatory duct several cm. Visualization of the right vas was unsuccessful because the injected contrast medium was not dense enough to show any outline although several cubic centimeters of fluid were injected. It was decided to surgically explore the scrotum under local anesthesia and attempt retrograde injection of the vas to determine the patency of the lumen. The right scrotum was first explored. The testis and epididymis were entirely normal but after careful search and exploration of the cord no evidence of a vas deferens could be found. The globus minor of the epididymis simply ended in a collection of small tubules. The patient would not permit an exploration of the left scrotum at that time and did not return for further studies.

vas deferens must first be understood. The ductus epididymis of the epididymis, vas deferens, seminal vesicles, trigone and ureters are all of pronephric origin.

Later in the 4 mm. embryo the pronephric duct remains and becomes the mesonephric duct which begins to elongate away from its cervical site downward to join the cloaca (fig. 1). At the site of this union with the cloaca the primitive ureters appear as separate outbuddings, or evaginations from the now mesonephric (wolffian) duct. The cranial or the upper end of each mesonephric duct in the male

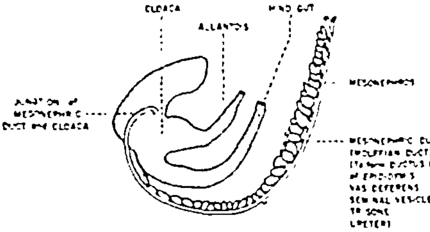

FIG. 1. Relationship of mesonephros and mesonephric duct to cloaca in 4 mm. embryo. Mesonephric duct becomes the wolffian duct from which is eventually formed ductus epididymis of epididymis, vas deferens, seminal vesicles and ureters. Fusion of mesonephric duct in region of the cloacal junction forms trigone.

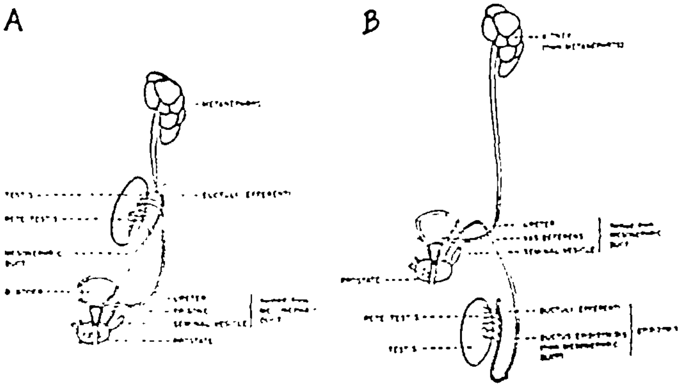

FIG. 2.A, situation and relationship of testis and its excretory channels in embryo during second trimester. Ductuli efferenti from mesonephric duct have joined rete testis of testicular anlage. It is these that form epididymis. Note post-ureteral location of vas deferens. Ureteral bud has grown cranial and anterior to terminal vas deferens (original mesonephric or wolffian duct).

B, schematic drawing at birth. Testis has descended anterior to ureter and epididymis has fully formed. Vas deferens has now crossed ureter on its anterior aspect.

unites with the seminiferous tubules of the testicle through the upper mesonephric tubules (wolffian body) which do not degenerate. These persisting mesonephric or connecting tubules form the ductuli efferenti of the epididymis. That portion of the mesonephric duct below the ductuli efferenti becomes markedly convoluted and forms the remainder of the epididymis. The mesonephric duct itself persists as the vas deferens (fig. 2, A). The testis leaves its upper abdominal position and after its descent is complete, the epididymis lies caudal to the ureters (fig. 2, B).

Because the epididymides, trigone and ureters were present in each of these cases associated with either absence or possible atresia of the vas deferens,

endoscopic means is emphasized. We believe, in the vast majority of instances that the probable embryological cause for this malformation to be secondary atresia or degeneration of the mesonephric (wolffian) duct or vas deferens in its middle portion after it has once formed.

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third of the patients with known fistulas to the bladder can a communication be disclosed radiographically.

The treatment of vesicocolic fistula is surgical. The safest procedure in the majority of instances is a multiple stage operation consisting of preliminary colostomy followed in 60 to 90 days by resection of the sigmoid and closure of the vesical opening. Restitution of bowel continuity is the final stage. Recently, primary resection of the sigmoid with or without colostomy has been used with success, due to our new and more potent antibiotics. The activity of the inflammatory process as well as the extent of the involvement will determine the safest procedure. It is not enough to merely divide the fistulous tract and close the openings in the bowel and bladder. When this is done sutures are inserted into infected tissues and recurrences are frequent.

Other types of urinary tract involvement occurring at times with diverticulitis of the colon are: *acute urinary retention* as demonstrated in case 1 and *lower ureteral obstruction* as evidenced in case 2.

Case 1. G. S., No. 9076, a 72 year old white man with a past history of two prostatectomies elsewhere, was admitted to the Brooklyn Hospital complaining of lower abdominal and rectal pain of 36 hours' duration associated with inability to void. There was tenderness in the left lower quadrant, a markedly distended bladder and roentgen evidence of gas under the diaphragm. A diagnosis of ruptured diverticulum of the sigmoid was made. Surgical exploration revealed intra- and extraperitoneal perforation of a diverticulum of the colon. There was marked edema and induration of the retroperitoneal tissues in the region of the vesical neck. The sigmoid was repaired and the patient made an uneventful recovery.

Case 2. A. L., No. 3960, a 34 year old white man, was admitted to the Brooklyn V. A. Hospital complaining of dysuria, burning, frequency, left flank pain and questionable pneumaturia. Examination disclosed an area of marked narrowing in the sigmoid (fig. 1, *A*) and a filling defect in the lower one-third of the left ureter. Surgical exploration revealed a mass in the pelvis (inflammatory by biopsy) involving the sigmoid and the urinary bladder. A transverse colostomy was done and 60 days later repeat roentgen examination of the sigmoid showed marked improvement of the mucosal pattern (fig. 1, *B*) and several small diverticula. Urograms showed that the previously seen constant filling defect in the left lower ureter (fig. 1, *C*) had disappeared and only a slight residual narrowing persisted (fig. 1, *D*). At secondary surgical exploration the sigmoid was found to be adherent to the bladder with a small fistulous tract. We observed an almost complete subsidence of the marked inflammatory process encountered at the time of the original operation. The involved portions of the sigmoid and bladder were resected and the fistulous tract excised. The colostomy was closed at a later date. One year later the patient reports that he has experienced no further urinary symptoms.

In both these cases the urologic involvement with its accompanying symptoms was brought about by exudative and productive inflammatory changes in the retroperitoneum, the exciting focus being a perforating infected diverticulum of the colon. In the first case, these inflammatory changes caused an acute displacement of the bladder neck resulting in an inability of the patient to in the second case, the ureter was enclosed in and infiltrated by the inflammatory products causing symptoms of urinary tract infection and obstruction.

When pneumaturia and fecaluria are present the diagnosis of fistula between the urinary bladder and some portion of the bowel is obvious. It then remains only to ascertain the etiology and location. The problem, as we see it, is to consider and to investigate the possibility of diverticulitis of the colon wth perfora-

tion may give rise to atypical manifestations or even escape detection only to manifest itself later as a retroperitoneal or perinephric suppuration.

The characteristic findings which aid in the differentiation of a suppuration of this etiology from that having its origin in the kidney are as follows: 1) the presence of gas in the region of the abscess cavity on roentgen study; 2) the finding of coliform organisms in the cultured pus; 3) the presence of the major portion of the suppuration in the region of the true pelvis; and 4) the tendency to recurrences.

The symptoms may include chills, fever, pain in the right lower quadrant, right upper quadrant or flank, tenderness with or without a mass in the same area. There may be blood and pus in the urine. The urograms may reveal displacement of the ureter in the region of the appendix or if there is distant spread of the suppuration one may find the classical signs of a perinephric abscess. Roentgenographic studies of the bowel may be of little value except in ruling out such diseases as regional enteritis.

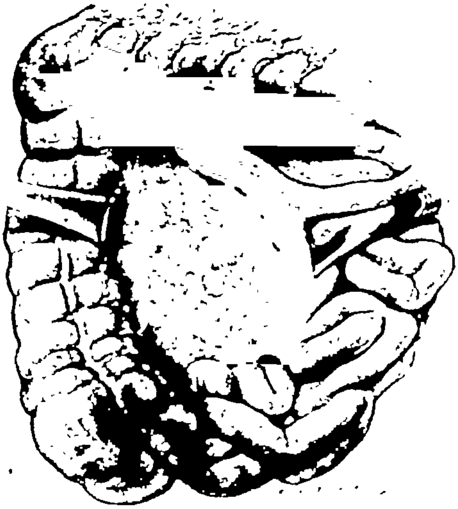

FIG. 2. Artist's interpretation of process at time of original operation. Retrocecal and retroperitoneal appendix with perforation resulting in multilocular retroperitoneal and perinephric abscess that caused medial displacement of right ureter.

Case 3. T. E. W., No. 6237, a 34 year old white man with a past history of having "pus removed from around the right kidney" twice in less than 1 year, was admitted to the Veterans Administration Hospital *complaining* of chills, fever and pain in the right flank. Complete remission of symptoms and findings had followed each previous operation. Surgical intervention disclosed a large multilocular retroperitoneal abscess which extended from the perinephric area to the iliac fossa. The locules were broken, and the pus evacuated yielded E. coli on culture. Three months following the last drainage of the abscess an [illegible]

terized pathologically by an ulcerative, granulomatous, stenosing type of presenting diversified manifestations. In order of frequency the clinical forms terminal ileitis; jejuno-ileitis; migrating colitis, wherein the terminal ileum involved along with a portion of large bowel; colitis, wherein a segment of la bowel alone is involved.

The diseased portion of bowel may perforate into the urinary bladder or i the retroperitoneum. The former occurrence is probably the best known of t complications, and yet this is infrequent in its own right. The symptoms a findings vary depending on the stage and the severity of the process and may

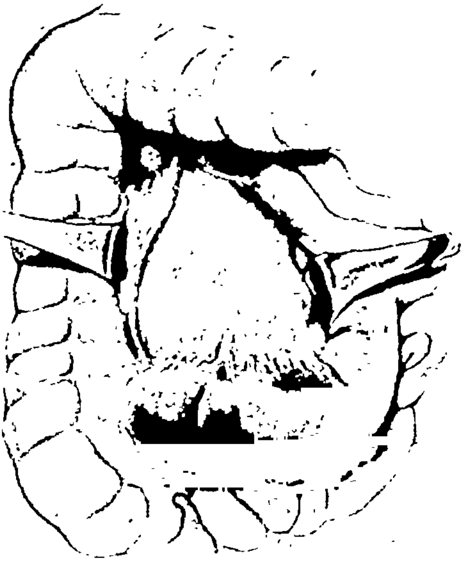

FIG. 4. Artist's interpretation of process at time of admission to hospital. Reg enteritis. Retroperitoneal perforation of diseased terminal ileum resulting in multil retroperitoneal abscess and lateral displacement of right ureter.

indistinguishable from those arising from and described under diverticulit the sigmoid colon. Perforation into the retroperitoneal tissues may result in formation of a retroperitoneal abscess which may include the perinephri sues. The symptoms and findings may be identical with those described u extraperitoneal appendicitis.

Extraperitoneal perforation may be of a less acute form so that the uri aspect of this syndrome persues a chronic course. The resulting changes in urinary tract are those representing a distinct *intestino-urinary syndro* lytic and inflammatory process from the intestine may involve the perin structures and the ureter by compression or actual invasion. Urograms, i experience, depending on the extent of the process will show displacem

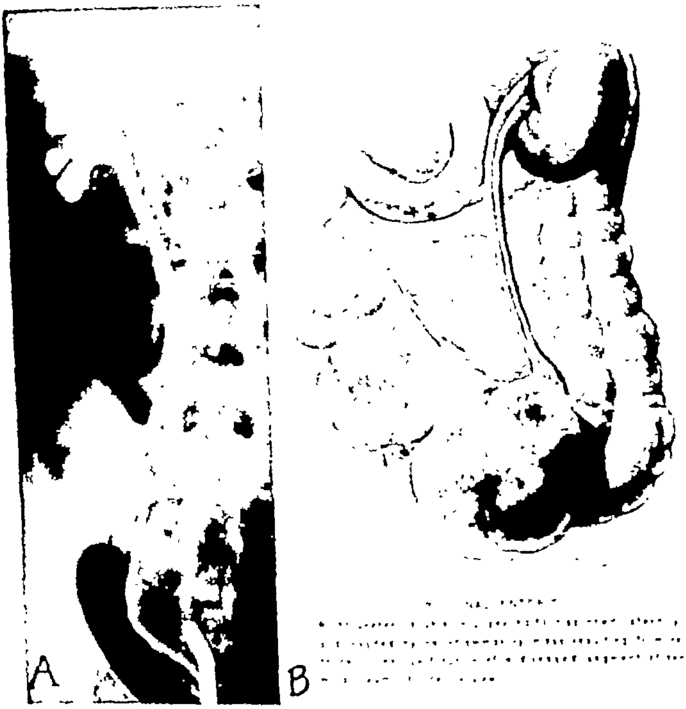

Fig. 5. A, urogram shows right double kidney with double ureters which joined to form common ureter in region of sacro-iliac joint. Ureters as well as pelves were moderately dilated, and common ureter just distal to point of juncture was irregularly narrowed. B, posterior view of operative findings. Right ureter (double in upper half) displaced laterally and invaded by inflammatory mass resulting from retroperitoneal perforation of diseased segment of terminal ileum

TABLE 1. *Regional enteritis*

PATIENT	SYMPTOMS	GENITO-URINARY ROENTGEN FINDINGS	FINDINGS AT OPERATION	OPERATIVE PROCEDURE	RESULTS
P. W. No. 178 Age, 63	Pneumaturia, fecaluria, abdominal cutaneous fistula	Normal	Terminal ileum and cecum adherent to each other and to urinary bladder. Three separate areas contribute to formation of cutaneous fistula (fig. 3).	Resection of terminal ileum and cecum plus ileo-ascending colostomy. Excision of cutaneous sinus tracts and fistulous tract to bladder. Excision of portion of bladder with primary closure.	No recurrences 18 months later.
S. T. No. 789 Age, 26	Recurrent right retroperitoneal abscess; three times during two-year period.	Lateral and anterior displacement of right lower ureter.	Multilocular retroperitoneal abscess (operation 1). Thickened terminal ileum adherent to and perforated through posterior peritoneum (operation 2, fig. 4).	Evacuation of multilocular retroperitoneal abscess (operation 1). Ileo-ascending colostomy with exclusion of distal ileum (operation 2).	Two-year follow-up; no recurrence of retroperitoneal abscess; no bowel symptoms.
M. K. No. 1243 Age 32	Right flank pain radiating, on occasion to right testicle. Dysuria. Diarrhea.	Dilated right double ureters and renal pelves, the former joining at the level of the sacro-iliac joint. The common ureter distal to the point of juncture was irregularly narrowed for a distance of approximately 6 cm. (fig. 5, *A*).	Inflammatory terminal ileum had perforated through the posterior peritoneum, involving the common right ureter in the inflammatory mass (fig. 5, *B*).	Exploration of right ureter with insertion of T-tube: exploratory laparotomy (operation 1). Nephro-ureterectomy (operation 2). Ileo-transverse colostomy with excision of ileitic process (operation 3).	Course satisfactory; initial intervention in the genito-urinary tract, due to incorrect diagnosis, led to loss of kidney.
H. E. No. 1353 Age, 32	Loss of weight, diarrhea; right flank pain radiating, on occasion, to right testicle	Medial displacement of mid portion of right ureter with a 4 cm. area of dilatation proximal to this displacement and a narrowing above the level (fig. 6, *A*).	Involvement of two areas of both ileum and jejunum, with dilatation of the entire small bowel. Lower portion of jejunum is adherent to posterior peritoneum at site of perforation.	Jejuno-transverse colostomy.	Gain in weight and marked improvement of bowel movements. No recurrence of genito-urinary symptoms. Return of ureter to normal (fig. 6, *B*).

cystitis, vesico-enteric fistulas, vesicocolic fistulas and bladder neck displacement due to extrinsic pressure are described.

Treatment is presented and one main overall point is stressed, namely: aside from evacuation of frank pus, which should have first consideration, active therapeutic treatment should be directed towards the bowel. The urinary complication will usually disappear after bowel surgery and regression is to be anticipated in all but the very chronic cases since the major pathologic process is not intrinsic in the urinary tract.

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RESULTS OF STREPTOMYCIN THERAPY IN URINARY TUBERCULOSIS: A FOUR YEAR REVIEW

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Antibiotic treatment of tuberculosis has afforded a new hope to countless sufferers from this disease; particularly those persons in whom the disease has spread from the primary focus to involve the skeletal system, the urogenital tract or other areas. Favorable results have been reported from many institutions that have used these new agents. At the present time there is no determinative knowledge regarding the optimal dosage or duration of antibiotic therapy; nor is it yet known whether streptomycin is more effective than dihydrostreptomycin. Likewise there is at present a lack of knowledge regarding the effectiveness of adjunct chemotherapy with agents such as para-amino-salicylic acid. These and other factors will be determined only after long term observations have been made. The Veterans' Administration program under the direction of Dr. John Barnwell is carrying out a large scale program that is carefully controlled and will go a long way in the final evaluation of various therapeutic regimens. Their patients are almost exclusively young males. Civilian institutions will provide data on other segments of the population and so will be helpful in the eventual assay of methods.

Seventy-three patients have received antibiotic therapy in the University of Michigan Hospital since 1946. The present report is based on 64 of these who have been followed a minimum of 6 months after the completion of the therapeutic regimen.

The employment of antibiotics has not radically changed the method of treating urinary tuberculosis in this clinic. They have been used to augment well established principles of treatment. Sanatorium care during and for 6 to 12 months following antibiotic therapy has been considered to be imperative in the treatment of urinary tuberculosis as in other types of the disease.

All cases are first evaluated by cystoscopy and retrograde pyelography, renal function study; and culture and guinea pig inoculation of the separate kidney as well as bladder urine specimens. Having established the presence or absence of destructive lesions, treatment is begun. If no gross lesions are evident by x-ray a 90 day course of treatment and sanatorium care is given following which another complete evaluation with pyelographic studies is made.

In the event of a small or moderate sized unilateral destructive lesion the patient is started on the antibiotic regimen and re-evaluated after 30 days. If there is no evidence of substantial improvement the affected kidney is removed and the course of antibiotic treatment is completed. Patients having severe renal destruction in one kidney are subjected to nephrectomy soon after the beginning of therapy, then the 90 day course is completed. All patients have complete check-up examinations every 3 months for 1 year; every 6 months thereafter.

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to our series for other investigations have observed the same clinico-laboratory paradox. One is again reminded that careful laboratory control, though an essential to good clinical investigation, has inherent fallibility, for bacteria do not always act the same in a living host as they do in the test tube.

Table 2 summarizes the results of treatment in patients having bilateral renal tuberculosis. It will be noted that 13 of the 21 bilateral cases had one kidney removed. Nine of these had previous nephrectomy and suffered from involvement of the remaining kidney. Four patients with bilateral disease had advanced cavitation in one kidney while the other was x-ray negative: they were nephrectomized and treated with antibiotics. Eight of these 13 nephrectomized bilateral cases have remained well since treatment.

TABLE 2. *Bilateral renal tuberculosis*

RENAL STATUS	TOTAL	REMISSION
Previous nephrectomy, normal x-ray	7	5
Previous nephrectomy, abnormal x-ray	2	1
Nephrectomy with treatment	4	2
No previous nephrectomy	8	4
	21	12=58%

TABLE 3. *Unilateral renal tuberculosis*

RENAL STATUS	TOTAL	REMISSION
Normal x-ray	8	7
Abnormal x-ray	6	2
Abnormal x-ray and nephrectomy	15	12
Total	29	21=73%

Eight bilateral cases had antibiotic therapy alone and 4 have had remissions lasting to the present date. Thus, 12 of the 21 bilateral cases (58 per cent) have had a favorable response to treatment.

Table 3 is concerned with 29 cases of unilateral kidney tuberculosis. Fifteen of this group were treated by nephrectomy in conjunction with antibiotic therapy. Nephrectomy in all these cases was selected either because the renal involvement was advanced or else because a lesser extensive lesion failed to demonstrate a satisfactory response during antibiotic treatment. Twelve responded favorably and have remained free from relapse.

Fourteen patients with unilateral disease were treated with antibiotics alone. Six were x-ray positive; two have responded satisfactorily to treatment. Eight unilateral cases that were x-ray negative were treated and only one has been a failure to date. Thus, 21 of 29 patients (73 per cent) with unilateral disease have responded favorably to our modern technique of therapy. It is a significant fact that x-ray negative kidneys have shown a high incidence of remission whereas kidneys with destructive lesions have rarely responded.

hydronephrosis), and 8 of these (44 per cent) responded favorably and have remained in remission. No cases with large caseating lesions showed healing or became tubercle bacilli free. However, some kidneys that showed extensive cicatrization have responded spectacularly.

Among the 64 patients in the series there have been observed a total of 27 failures or relapses following the first course of therapy. Twenty of these received a second course of treatment either because they failed to respond to the first course or else relapsed following a temporary remission. Two of the 20 receiving a second course failed to respond at all and 11 of the remaining 18 have relapsed at some time since the second course of treatment. The rate of the entire 40 instances of relapse or failure have been charted in order to demonstrate the time of occurrence following antibiotic therapy (fig. 1).

In treating a disease that is characterized by its chronicity as well as by its tendency to relapse, it is manifestly necessary to reserve judgment until long-term observation of cases has been possible. In the present series we have observed that 70 per cent of the cases at present are enjoying freedom from clinical evidences of urinary tract tuberculosis. It must be assumed that some of these will eventually relapse; how many, only time will reveal. In this series of cases there are 17 who have been followed for 3 years or more and 7 are well (41 per cent). Thirty-two have been followed 2 years or more and 14 of this group (44 per cent) are in remission. These data do not indicate survival rates alone but rather patients who are both alive and whose urines are free from tubercle bacilli.

It is obvious that antibiotics have a useful and important *role* in the treatment of urinary tuberculosis; 70 per cent of the present series became bacteria free after treatment. Experience has shown that large dosages of streptomycin or dihydrostreptomycin are more effective than small amounts; and that the regimen should be carried for 90 days or more. It is our belief that these principles should be followed in all cases, and that the employment of a less vigorous regimen is a deplorable compromise in the treatment of this serious disease.

When gross caseation in one kidney is demonstrated by pyelography such a kidney should be removed after a fortnight of preoperative medication, then the antibiotic regimen should be continued for at least 90 days.

Kidneys that are known to be tuberculous yet are x-ray negative or show only minimal destruction should be treated for a month with antibiotics if the lesion be unilateral. If, then, the affected kidney shows substantial improvement by urinalysis and by x-ray the antibiotic regimen should be carried on to its completion and then another survey can be made. If, after 30 days of treatment, the kidney fails to show marked improvement it should be removed and therapy be continued to its conclusion.

As a result of our observations on this group of patients, we feel that, although streptomycin is not a panacea for renal tuberculosis, it certainly is a welcome adjunct to the armamentarium used in the treatment of this disease. No cure can be given those so afflicted and the use of streptomycin appears to enhance the patient's chance for an arrest of this otherwise discouraging disease.

used in concentrations varying from 0.1 to 100 micrograms per ml of medium and neomycin hydrochloride* in concentrations varying from 0.1 to 500 units per ml. Inoculation of the tubes containing 10 ml of the medium-antibiotic mixture was achieved with 0.1 ml of a suspension of the various strains of PPLO. The suspensions were prepared by grinding agar blocks containing 48 hour growth of the organisms in 5 ml of Bacto-heart infusion broth. The supernatant formed after the agar particles had settled was used as the inoculum. The same suspension was used for inoculating the various tubes for each particular strain. Control tubes without any of the antibiotics were also included. Incubation was carried out aerobically at 37C for 3 and 5 days. At the end of these periods a standard 4 mm. platinum loopful was subcultured from each tube onto the foregoing solid medium. After 48 hours incubation under the same conditions the plates were examined with a low power of the microscope. Observation was made as to whether the growth was maximal as in the control plate or whether some inhibition occurred.

The amount of antibiotic remaining in the active state, in the case of terramycin, was determined by assaying the tubes after the three day incubation period. The method was that described by Herrell et al. using bacillus No. 5† as the assay organism.

The clinical evaluation of terramycin and streptomycin was performed on patients presenting themselves at the Urology Clinic of the Hospital of the University of Pennsylvania and private patients of one of us (P.R.L.). In all the cases cultures taken prior to therapy were found to be infected with PPLO. A series of two or three cultures was made for a period extending over one to four months after treatment. Clinical observation was also continued over this time. All patients treated with streptomycin were hospitalized during therapy because of the administration of the antibiotic intramuscularly and also in the event of the appearance of toxic reactions. The terramycin was administered orally.

RESULTS

In vitro. Both terramycin and neomycin were effective in inhibiting the growth of PPLO. The concentrations of the two antibiotics which prevented the growth of PPLO are given in table 1. Terramycin was the better inhibitor, preventing growth of one strain at a concentration of 0.1 microgram and of seven strains at a concentration of 0.5 microgram per ml of medium. With this antibiotic the strains maintained on artificial medium for a long period of time did not show greater resistance to antibiotic action, as they did with neomycin and those other antibiotics reported previously (Leberman, Smith and Morton). Neomycin is required in higher concentrations but is effective at 6.25 units per ml of medium. The toxicity of neomycin at present limits its use in clinical infections. Terramycin on the other hand, on the basis of in vitro tests, appears to be of greater value for infections with PPLO than any antibiotic yet tested. Previously streptomycin was apparently the only antibiotic effective against all strains of PPLO

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*The neomycin was kindly supplied by Dr. Charles Mann, Heyden Chemical Corporation, Princeton, New Jersey

† Kindly supplied by Dr. W. E. Herrell, Mayo Clinic, Rochester, Minn

Herrell et al. likewise noted that oral administration of 1 to 1.25 gm. of te- ramycin every 6 hours gave therapeutic serum levels which were maintained at a constant level. Large amounts of this antibiotic are excreted in the urine and feces. Terramycin is readily diffusible through the placenta but only a trace is found in the cerebrospinal fluid.

Since *in vitro* tests revealed that PPLO were inhibited by a concentration of 0.5 microgram per ml of medium, the clinical effectiveness would seem appar-

Although thus far only 7 cases have been treated with terramycin, all have responded. The advantages of low toxicity, oral administration and high anti- biotic activity against PPLO appear to make terramycin the antibiotic of cho- in the treatment of infections caused by the pleuropneumonia-like organisms. This is being substantiated by work which is in progress.

SUMMARY

Terramycin hydrochloride inhibited growth of eight human strains of pleuro- pneumonia-like organisms in the concentrations of 0.5 microgram per ml of medium while neomycin hydrochloride was required in concentrations varying from 2.0 to 6.25 units per ml. of medium.

Three patients infected with pleuropneumonia-like organisms, two of whom had Reiter's syndrome, became asymptomatic and were free of the organisms after streptomycin therapy.

Terramycin likewise brought about rapid disappearance of the organisms and clinical remission of symptoms in seven cases of genito-urinary infections caused by pleuropneumonia-like organisms. Terramycin appears to be the antibiotic of choice for the treatment of infections with the pleuropneumonia-like organisms.

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areas which, when sectioned exuded a pink creamy material. Histologically the lesions exhibited central aggregates of lymphocytes, granulocytes, lipid-filled macrophages and unfilled macrophages. Peripheral to these cells were irregular globules of fat with scattered lipid macrophages at the edges of the globules (fig. 2, *A*).

Two weeks after injection the perirenal and peri-ureteral tissue exhibited a suet-like appearance. Sections were typical of sclerosing lipogranuloma showing varying sized globules of fat separated by large numbers of lipid filled histiocytes and septa of fibrous connective tissue. Foreign-body giant cells and scattered lymphocytes dotted these septa. Endothelial cells surrounding the fat globules were present but not conspicuous.

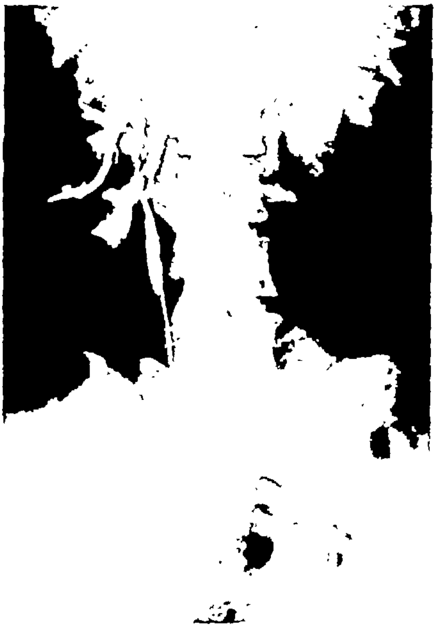

FIG. 1. Perirenal and peri-ureteral extravasation of contrast medium introduced through nephrostomy catheter.

At the end of 4 weeks the peri-ureteral fat at the site of diodrast injection was replaced by dense, grayish-white rubbery tissue which on microscopic examination consisted of a dense mat of proliferating fibroblasts showing scattered foci of calcification with scattered intervening lipid-filled macrophages and foreign-body giant cells (fig. 2, *B*).

The occurrence of calcification was most interesting since, as Smetana and Bernhard have pointed out in their exhaustive treatise, this is not characteristic of sclerosing lipogranuloma.

Recently a kidney removed surgically because of multiple calculi was examined and found to have the same gross and microscopic peripelvic changes as were observed in our experimental animals. Sections of the peripelvic tissues showed lipogranulomatous changes consisting of central areas of hyalinized [illegible]

surrounded by foreign body giant cells and lipid-filled macrophages (fig. 2, c). The preoperative retrograde pyelograms were then examined. They revealed peripelvic extravasation of contrast medium.

DISCUSSION

Our findings leave no doubt about the florid sterile inflammatory reaction, sclerosing lipogranulomatosis and subsequent fibrosis brought on by extravasation of urographic contrast medium.

Peri-ureteral leakage occurs most frequently at the site of incisions into the ureter and pelvis. Since these incisions are made at points of obstruction such as ureteropelvic or ureteral stenosis or at the points of narrowing where the progress of a stone is arrested, it can be seen that leakage of contrast medium at these sites may nullify the desired result for which surgery was performed.

It is therefore suggested that early postoperative urography be performed with caution and that small quantities of dilute contrast medium be used, at least at first, until the capacity of the structures to be visualized is determined. We also suggest that care be used in retrograde pyelography if there be any question of perforation of the ureter or pelvis.

SUMMARY

Clinical and experimental data are presented to demonstrate the occurrence of sclerosing lipogranuloma and peri-ureteral fibrosis following extravasation of aqueous urographic contrast medium. Mention is made of safeguards against this complication.

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Smetana, H. F. and Bernhard, W.: Sclerosing lipogranuloma. Arch. Path., 50: 2[illegible] 1950.

histadyl, an antihistaminic preparation, was administered intravenously. After 25 minutes, when still neither the blood pressure nor the pulse could be obtained, the patient was transferred to the hospital by ambulance, oxygen therapy being continued. There he was placed in an oxygen tent, an intravenous infusion of 1000 cc of 5 per cent solution of glucose in physiologic solution of sodium chloride containing 1 ampule of a 1 to 1000 solution of epinephrine was started, and 100 mg. cortisone given intramuscularly. It was not until 1½ hours after the injection of neo-iopax, and 15 minutes after the infusion, that a faint pulse at the wrist could be felt and a systolic blood pressure of 50 mm. of mercury could be obtained. From this time on the patient made satisfactory progress and he was discharged from the hospital the following day. He did not feel well enough to return to work, however, for four more days.

DISCUSSION

Such an occurrence brings to mind several questions: What happened? Can such reactions be predicted? What can be done to prevent their occurrence? What is the best method of treatment?

Clinically, anaphylactic and anaphylactoid reactions are indistinguishable. Anaphylactic reactions are predicated on an immunologic mechanism. Anaphylaxis is a special type of induced sensitivity to proteins or haptenes resulting from the introduction of an allergenic substance into a previously sensitized organism. The substance producing anaphylactic shock may be introduced by any route. On the other hand, an anaphylactoid reaction—sometimes termed "colloidal shock"—is thought to be based on a physiochemical reaction, and occurs generally after the material is introduced by the intravenous route. The type of reaction may be differentiated further in that in anaphylactoid reactions there is no incubation period, no insensitive period after the reaction, no passive transfer or a Schultz-Dale phenomenon, and the shocking material may be a chemical substance. It is stated that, in anaphylactoid deaths, multiple emboli and capillary thromboses—especially in the lungs—are found, while in anaphylaxis, edema and hemorrhage into the pulmonary tissues are more frequent.[1] In the case reported here, it cannot be said whether or not the neo-iopax became conjugated in the blood stream to form a haptene and produce a true anaphylactic reaction.

Prediction as to reaction is based on the history of the patient and on his reaction to tests of various types. Singer,[2] reporting a series of 160 cases in which diodrast was used, stated that reactions to this substance were more frequent among those with allergic backgrounds, either personal or familial. This may also be true for neo-iopax. Furthermore, it may be predicted that, in persons who have previously experienced a severe reaction to the medium, its repeated use would constitute an even greater risk.

Oral, cutaneous and conjunctival tests have been used to determine sensitivity to contrast media; it would appear from the available literature that the

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[1] Topley, W. W. C. and Wilson, G. S. Principles of Bacteriology and Immunity. Baltimore: Williams & Wilkins, 1946, 3rd ed., vol. 2, p. 1112.

[2] Singer, A. G., Jr. Am. J. Roentgenol., 59: 727, 1948.

at a sufficient speed to raise the blood pressure out of the shock level. Subcutaneous administration of vasoxyl, a new sympathomimetic drug which gives sustained vasoconstriction, should be a useful adjunct. Cortisone may be of value on the theory that such a severe reaction could produce temporary "adrenal exhaustion." Since antihistaminics administered intravenously tend to lower the blood pressure even in normal persons, and since the damage due to release of histamine has, for the most part, already taken place, their value once a reaction has occurred is questionable; they are not, therefore, advocated.

It is probable that neo-iopax for intravenous study could safely be used within the next few days after a true anaphylactic reaction in view of the subsequent period of insensitivity which is produced. If the reaction were anaphylactoid in nature, probable retrograde injection of the substance could safely be done. If future studies are imperative and the type of reaction is not known, another type of contrast medium should be used, as specificity appears to be marked to various drugs, e.g., acetylsalicylic-acid sensitive patients are generally not sensitive to salicylic acid, methyl salicylate or to benzoic acid.[7]

SUMMARY

A case of severe reaction to neo-iopax is reported; this may have been either a true anaphylaxis or an anaphylactoid reaction.

Measures helpful in predicting severe reactions to contrast media are discussed. The history, the conjunctival reaction, and an intravenous test-dose may be of value. Prophylactically the oral use of antihistaminics and possibly the administration of aspirin prior to injection of the contrast medium would seem worthwhile.

To combat severe reactions, immediate intensive therapy is recommended in the form of intravenous administration of epinephrine, use of oxygen and of other measures to combat shock; supplies should always be available for immediate use. The value of cortisone in cases in which the patient does not die immediately is suggested.

The feasibility of excretory or retrograde urography following severe reaction to a contrast medium is considered.

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ADDENDUM

Since this paper was submitted for publication, an article by Getzoff[8] has appeared stating that deaths following the administration of neo-iopax have been reported by Daut and Dunn,[9] French,[10] and in the editorial column of a

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[7] Landsteiner, K., *The Specificity of Serological Reactions*, Cambridge, Mass., Harvard University Press, 1947, p. 206.

[8] Getzoff, P. L., J. Urol., **65:** 1139, 1951.

[9] Daut, R. V. and Dunn, J. H., J. Urol., **61:** 1091, 1949.

[10] French, L.: Bull. Univ. Minn. Hosp., **20:** 18, 1949.

aphasic and perspired profusely; his pupils dilated and the systolic blood sure exceeded 260 mm. Hg. The blood pressure remained at this level minutes, then gradually approached the resting level. While there were ap- ently no immediate ill effects following this procedure, 4 days later the pa complained of pain in the right abdomen, nausea and vomiting. Examina disclosed a blood pressure of 255/190, right abdominal tenderness and hema Twenty-four hours later the patient was febrile and almost completely Extreme retinal pallor was noted bilaterally.

FIG. 1. Case 1. Retrograde pyelogram interpreted as showing normal upper uri tract.

Nine days after the etamon test, 18 mg. piperoxane hydrochloride (benod was given intravenously after the blood pressure had stabilized at 154/11 without any change in blood pressure or development of untoward symp Two days later, 500 mg. N,N-dibenzyl-beta-chloroethylamine (dibenamin administered intravenously over a 70 minute period. In 110 minutes, the pressure had decreased from 170/110 to 90/70.

As the patient's symptoms and response to a provocative test were sug of chromaffinoma, an exploration of the adrenal glands was deemed advi

Under ether endotracheal anesthesia the right adrenal gland was exp through a thoraco-abdominal incision in which the last two ribs were re This afforded extremely good exposure of the adrenal area, and a normal was found. Except for a rise to 280/180 at the time of intubation, the pressure remained in the preoperative range for the duration of the op

by spinal anesthesia or by subcutaneous ephedrine, it was believed that a epinephrine-producing tumor might be present. The basal metabolic rate was +23 per cent. The fasting blood sugar level was 85 mg. per cent.

Histamine, .025 mg. when given intravenously, had no effect on the blood pressure. Five days later, .050 mg. histamine was given. The blood pressure rose within two minutes from 138/86 to 162/100 and the patient complained of a pounding headache. The blood pressure gradually returned to the resting level in 10 minutes.

Immersion of the patient's hand in ice water caused no change in pulse rate or blood pressure.

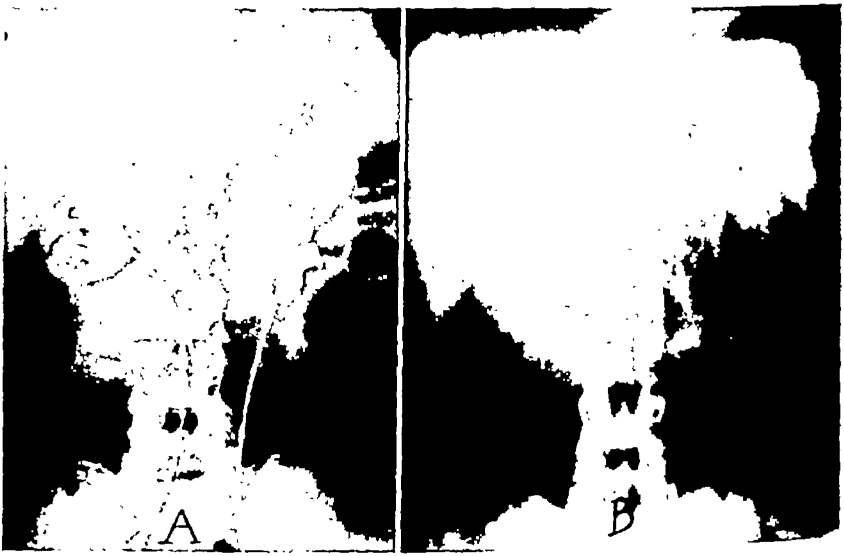

FIG. 2. Case 2. *A*, retrograde pyelogram showing incomplete rotation of left kidney [illegible] medial deviation of middle of right ureter. This is interpreted as representing [illegible] horseshoe kidney. *B*, laminogram following perirenal insufflation of air on left shows [illegible] mass above and medial to upper pole of left renal shadow opposite body of first [illegible] vertebra.

Because of progressive T wave changes in postoperative electrocardiograms and because the patient complained of dyspnea and a feeling of constriction [illegible] the chest during exercise, it was felt that myocardial infarction had taken place, most likely at the time of the extreme hypertension that had occurred during surgery. Further provocative tests for pheochromocytoma were felt to be [illegible] dangerous at this time; the patient was allowed to leave the hospital for [illegible] months.

At the end of 3 months, an electrocardiogram showed only left ventricular strain. Etamon 100 mg. was given intravenously after the blood pressure had stabilized at 132 96. The blood pressure quickly rose to 196 40, then to 210 [illegible] When the patient was raised to a sitting position, the pressure quickly fell to 120 84. The injection of .025 mg. histamine produced an elevation of [illegible] from a resting blood pressure of 140 102. The intravenous injection of [illegible]

aphasic and perspired profusely; his pupils dilated and the systolic blood pre sure exceeded 260 mm. Hg. The blood pressure remained at this level for 1 minutes, then gradually approached the resting level. While there were appar ently no immediate ill effects following this procedure, 4 days later the patien complained of pain in the right abdomen, nausea and vomiting. Examinatio disclosed a blood pressure of 255/190, right abdominal tenderness and hematuri Twenty-four hours later the patient was febrile and almost completely blind Extreme retinal pallor was noted bilaterally.

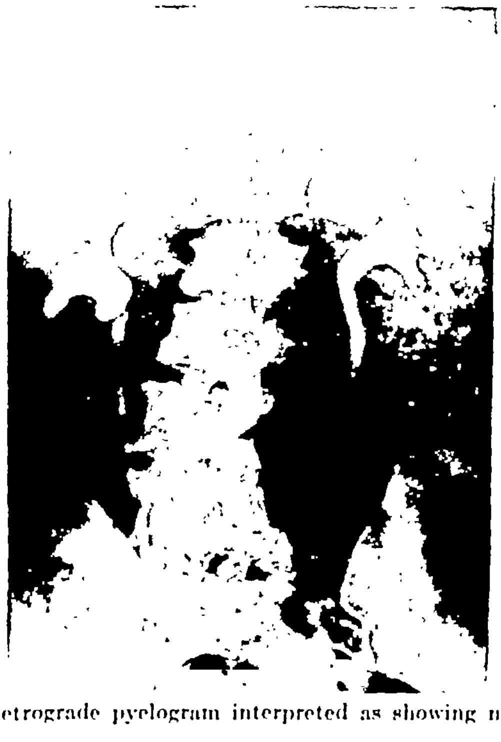

FIG. 1. Case 1. Retrograde pyelogram interpreted as showing normal upper urinary tract.

Nine days after the etamon test, 18 mg. piperoxane hydrochloride (benodaine) was given intravenously after the blood pressure had stabilized at 151/112, without any change in blood pressure or development of untoward symptoms. Two days later, 500 mg. N,N-dibenzyl-beta-chloroethylamine (dibenamine) was administered intravenously over a 70 minute period. In 110 minutes, the blood pressure had decreased from 170/110 to 90/70.

As the patient's symptoms and response to a provocative test were suspicious of chromaffinoma, an exploration of the adrenal glands was deemed advisable.

Under ether endotracheal anesthesia the right adrenal gland was explored through a thoraco-abdominal incision in which the last two ribs were resected. This afforded extremely good exposure of the adrenal area, and a normal gland was found. Except for a rise to 289/189 at the time of intubation, the blood pressure remained in the preoperative range for the duration of the operation.

by spinal anesthesia or by subcutaneous ephedrine, it was believed that an epinephrine-producing tumor might be present. The basal metabolic rate was +23 per cent. The fasting blood sugar level was 85 mg. per cent.

Histamine, .025 mg. when given intravenously, had no effect on the blood pressure. Five days later, .050 mg. histamine was given. The blood pressure rose within two minutes from 138/86 to 162/100 and the patient complained of a pounding headache. The blood pressure gradually returned to the resting level in 10 minutes.

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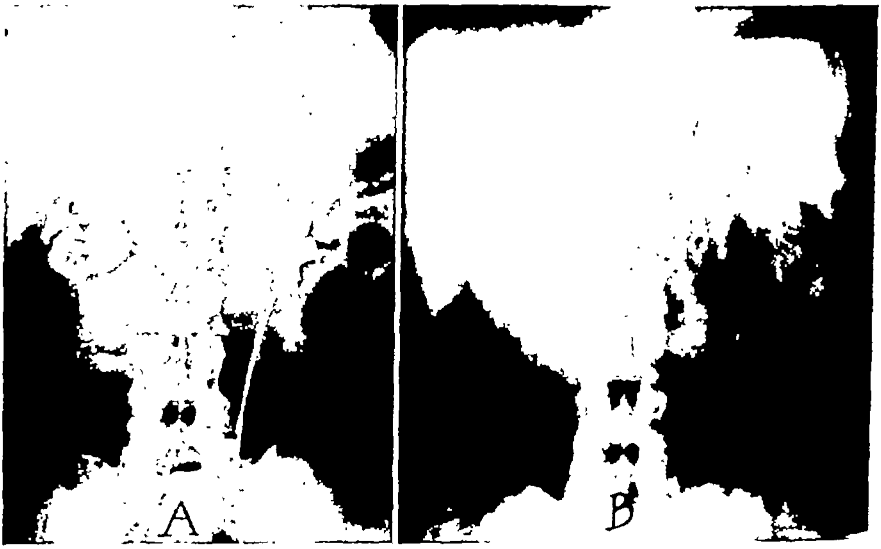

FIG. 2. Case 2. *A*, retrograde pyelogram showing incomplete rotation of left kidney and medial deviation of middle of right ureter. This is interpreted as representing fused or horseshoe kidney. *B*, laminogram following perirenal insufflation of air on left shows rounded mass above and medial to upper pole of left renal shadow opposite body of first lumbar vertebra.

Because of progressive T wave changes in postoperative electrocardiograms, and because the patient complained of dyspnea and a feeling of constriction in the chest during exercise, it was felt that myocardial infarction had taken place, most likely at the time of the extreme hypertension that had occurred during surgery. Further provocative tests for pheochromocytoma were felt to be too dangerous at this time; the patient was allowed to leave the hospital for three months.

At the end of 3 months, an electrocardiogram showed only left ventricular strain. Etamon 100 mg. was given intravenously after the blood pressure had stabilized at 132/96. The blood pressure quickly rose to 196/140, then to 210/136. When the patient was raised to a sitting position, the pressure quickly fell to 120/84. The injection of .025 mg. histamine produced an elevation of 178/134 from a resting blood pressure of 140/102. The intravenous injection of benodaine [illegible] caused no change in a resting blood pressure of 136/100. The administration of mecholyl 25 mg. subcutaneously had no significant effect on the blood pressure.

A left perirenal insufflation of air was done, injecting 300 cc of air under gentle pressure. Laminograms taken following this procedure outlined a round mass, about 4 cm. in diameter, above and slightly medial to the left renal shadow. The mass was not observed to cross the midline (fig. 2, *B*).

Through an incision which began in the eleventh left interspace in the posterior axillary line and curved forward and downward to the lateral border of the rectus sheath, a tumor of the left adrenal gland measuring 6.5 by 4 by 2 cm. was removed. Excellent extraperitoneal exposure was obtained by means of this approach. The blood supply of the adrenal gland was clamped and divided as it was encountered. The anesthesia consisted of ether and sodium pentothal. The blood pressure was quite variable during induction and intubation. During the operation, the blood pressure remained at 120/78 until the tumor was removed, at which time it fell to 100/70. A blood transfusion was started at this time.

The blood pressure was 80/55 when the patient was returned to his bed. Without medications, the blood pressure stabilized at 112/65 within 2 hours. The postoperative course was uneventful. On the thirteenth postoperative day, a normal electrocardiogram was obtained.

On the fourteenth postoperative day, the intravenous administration of etamon was attended by a rise in blood pressure from 130/90 to 191/138 within one minute. The pressure quickly fell to its starting point.

Because this test was inconclusive, the patient was recalled for further study in May 1951. He had worked steadily at hard labor in the interim, and felt well. He had noticed that he perspired much less than he did before removal of the tumor. Provocative tests with etamon and histamine were negative. Laminograms taken after perirenal insufflation of air on the right side demonstrated a normal renal shadow.

Microscopic examination of the tumor showed it to be made up of small groups of cells which varied greatly in size and shape, but averaged 15-20 micra in diameter, and which had a round vesicular nucleus and abundant lacy eosinophilic cytoplasm. The cell groups were separated by delicate, fibrous strands, which contained thin-walled vascular spaces. The diagnosis was pheochromocytoma of left adrenal gland.

of the blood pressure may be sustained for weeks or months. Paroxysms, whe they occur, vary in duration and intensity, lasting from a few minutes to man hours. They may be precipitated by emotional disturbances, exercise, changes i body position, injury, spinal anesthesia or any situation which might be expecte to cause a change in the blood pressure of a normal person.

Physical examination of patients who have a pheochromocytoma may revea a striking change in the pulse rate and blood pressure in response to changes i posture. The pulse rate in the standing position may exceed that in the recumben position by 20 or more beats per minute. The blood pressure in recumbency ma be 50 mm. Hg. higher than it is in the erect position, in both systolic and diastoli phases. This postural hypotension and tachycardia is most unusual in hypertension due to other causes.

The cold pressor test; that is, immersion of the patient's hand in ice water, is used in the evaluation of hypertension, and in most cases, results in an elevation of the blood pressure. If the hypertension is due to the presence of a pheochromocytoma, in most cases, a negative response will be obtained.

In a high percentage of patients who have an excess of circulating epinephrine, there are elevations in the basal metabolic rate, blood sugar level and body temperature. In fact, some of these patients have been treated for diabetes mellitus, with response to insulin in an occasional case. Glycosuria may occur during periods of elevated blood sugar level. Some patients respond to the glucose tolerance test with a diabetic type of curve.

Certain tests are used as additional evidence in the study of this disease. These tests are attempts either to precipitate an attack of hypertension during a normotensive phase in the patient, or to relieve an attack by specific drugs during a hypertensive phase in the patient.

Mecholyl 25 mg. when administered subcutaneously in a normal person, causes salivation, sweating, a slight transient fall in the blood pressure, followed by a mild sustained rise in the blood pressure. In a patient who has a pheochromocytoma, this drug causes the same symptoms except that after the slight fall in the blood pressure, the blood pressure rises to extremely high levels, and a typical hypertensive paroxysm may be reproduced. Not all patients with pheochromocytoma will show a response to this test.

The intravenous injection of 0.1 mg. histamine in a normal individual produces a fall in blood pressure, flushing of the face, and a more or less severe headache. If a pheochromocytoma is present, the fall in blood pressure may be followed by a typical hypertensive reaction. It is recommended that ¼ of the above dose be used first, followed by ½, followed by the full dose at intervals of several days, in order to prevent a dangerous paroxysm which may follow the full dose in an extremely susceptible patient.

Etamon, tetraethylammonium chloride, can be used as a provocative test for pheochromocytoma. An intravenous injection of 400 mg. has been recommended. In the normal person, or in a patient whose hypertension is not due to an excess of circulating epinephrine, there is a prompt fall in systolic and diastolic blood pressure, and an increase in the pulse rate to 100 120 beats per minute. In a [illegible] with a pheochromocytoma, this dose may precipitate a typical hyper- [illegible] paroxysm. To prevent the occurrence of a violent reaction, a dose of 100 [illegible] be tried first, and if this is inconclusive, a larger amount may be ad- [illegible] several days later.

The exact mechanism of action of these drugs in stimulating a hypertensive [illegible] a case of chromaffinoma is not completely understood. The side effects of [illegible] mecholyl, and histamine are unpleasant. The effect of etamon and his- [illegible] precipitating a hypertensive paroxysm in a case of pheochromocytoma [illegible] by sodium pentothal anesthesia, indicating that part of the stimula- [illegible] be of cerebral origin. Sedative drugs may render the effects of the drugs [illegible] and should not be used prior to a test.

[illegible] is a sympatholytic and adrenolytic agent which is related to the [illegible] mustards in its chemical structure. It may be used to determine if [illegible] is due to an excess of circulating epinephrine. In order to be of [illegible] the test must be done while the patient is in a hypertensive phase. [illegible] infusion of 500 cc normal saline solution is started, after the [illegible] been recumbent long enough for the blood pressure to become stabi- [illegible] A dose of 4-6 mg. per kilogram is then added to the saline solution and [illegible] mixed. This solution is allowed to enter the vein at a rate which will [illegible] administration of the entire 500 cc in 45-60 minutes. In a normal [illegible] patient with hypertension not due to excess of epinephrine, and in [illegible] with a pheochromocytoma in a normotensive phase, there will be no [illegible] In a case of hypertension due to a chromaffinoma, the blood pressure [illegible] a normal range within an hour. The effect of the drug may last [illegible] ever, are seldom conclusive. The use of air surrounding the adrenal glands as a contrast medium increases the diagnostic value of roentgenography greatly.

Perirenal air insufflation has been in diagnostic use for many years. The perirenal fascia envelops the kidney and adrenal gland, and extends downward along the ureter. The space contained within the fascia is roughly cone-shaped with the apex directed downward. The perirenal space is in direct continuity with the retroperitoneal space inferiorly and is in theoretical continuity with the space on the opposite side, around the great vessels. This connection is not always demonstrable. The technique is to inject 300–500 cc air under aseptic precautions into the perirenal space; serial x-rays are taken at 1–10 hour intervals for as long as 48 hours in some cases, depending on how long is required for the air to surround the adrenal gland. In some patients, the air will diffuse to the oposite side.

The injection of air into the retroperitoneal space to obtain contrast roentgenograms has recently been described. This procedure is based on the premise that the retroperitoneal areolar tissue is in direct continuity with the tissue which surrounds the pelvic organs, kidneys and adrenal glands. A needle is inserted through the skin about 2 cm. inferior to the sacrococcygeal joint, lateral to the coccyx. The needle is directed medially and superiorly, anterior to the sacrum, into the retro-rectal space. The needle may be guided by a finger in the rectum. After precautionary aspiration, 500 cc of air is injected and the needle withdrawn. X-rays of the abdomen are taken until the air has diffused to surround the adrenal glands. This method has the advantage that it is more likely to demonstrate the adrenal gland on both sides.

The diagnosis of pheochromocytoma must rest on a careful evaluation of all *available data in each individual case.*

The treatment of pheochromocytoma is removal of the tumor.

The adrenal gland is found above the kidney, in an anteromedial position. Its blood supply is derived from arteries at many points of the periphery. The greater number of these arteries also serve the neighboring structures, especially the kidneys and diaphragm. They comprise the superior capsular artery from the inferior diaphragmatic, the lessor capsular from the aorta, and the inferior capsular from the renal. These large vessels are divided into many small ones before entering the gland, the base of the gland receiving most of them. The adrenal arteries are most variable in their origin and distribution.

Chromaffin tissue is found in the adrenal glands, the paraganglia in association with the sympathetic ganglia, and in the organ of Zuckerkandl at the root of the inferior mesenteric artery. Tumor formation occurs in the adrenal gland in the vast majority of cases.

The surgical approaches to the adrenal gland will be mentioned. The advocates of the transperitoneal approach favor it because it allows for examination of both adrenal areas at the same time. The standard flank incision has the advantage of universal familiarity. It affords only fair exposure of the adrenal region. The posterior lumbar incision is not widely used, as it provides rather poor exposure. The thoracic, or thoraco-abdominal approach allows excellent exposure of the adrenal region. The proper approach is determined by the necessity of avoiding manipulation of the tumor before the blood supply is ligated.

In preparing the patient for operation, certain principles which are peculiar to this disease must be followed in addition to the general preoperative principles that apply to any surgical patient. Since hypertensive crises may be precipitated by emotional states, the patient must be carefully sedated prior to operation, not unlike the patient suffering from thyrotoxicosis. The anesthetic agent should be one which is least likely to cause a change in the blood pressure. Spinal anesthesia is not desirable. The patient may be given dibenamine intravenously 1–2 hours before operation, to prevent the development of hypertension incident to manipulation of the adrenal region, or a syringe filled with benodaine may be kept on the anesthesia table to be used in the event of untoward reaction during the induction of anesthesia or while the operation is in progress.

To avoid the liberation of dangerous quantities of epinephrine into the blood stream, the tumor should be handled as little as possible until the blood supply has been clamped.

Following removal of the tumor, the blood pressure may fall sharply. The use of vasopressor drugs at this point is to be condemned. The apparent lack of blood pressure may be due to an intense vasoconstriction caused by the liberation of a large amount of epinephrine inadvertently during the removal of the tumor. The effect would be similar to that of placing a clamp on the aorta. The administration of an epinephrine-like drug under these circumstances could be fatal. The fall in blood pressure can be controlled by the use of Trendelenburg position and transfusion of whole blood.

If an epinephrine-producing tumor is actively sought and properly treated in cases of hypertension, one more cause of high blood pressure may be added to the list of curable diseases.

An analysis of the 2 cases here presented is in order. In the first case, the presence of an epinephrine-producing tumor was suspected early in his study, and [illegible] tests were carried out with this in mind. The first provocative test with [illegible] was perhaps somewhat overenthusiastic, in that a fatality almost resulted from the full dose of the drug that was given. The lapse of four days [illegible] and the appearance of prolonged hypertension, blindness and [illegible] originally considered to be renal apoplexy cannot be accounted for. [illegible] indicate that the administration of etamon was not directly [illegible] the events which followed. It is much less dangerous to begin [illegible] and follow with a larger dose later, as was done in the second contraindicated. In case 1, in which epinephrine was used to combat hypotension following removal of the tumor, the blood pressure was extremely difficult to control, varying rather widely for an 8 hour period. In the second case, where no vasopressor drugs were used, the blood pressure presented no problem and was stable within two hours.

In case 2 a fused or "horseshoe" kidney was present. It is believed that this represents the first reported instance of the use of perirenal air insufflation in a patient with this anomaly.

SUMMARY

Because of the frequent association of the urinary tract with hypertension, the urologist is often asked to assist in the evaluation of the patient with an elevated blood pressure. For this reason, the urologist should be thoroughly familiar with the disease entity, *pheochromocytoma.*

This paper has presented in a practical form the symptoms, signs and diagnostic procedures characteristic of pheochromocytoma.

Two cases are presented to illustrate the methods of investigation in this disease.

One case is believed to be the first reported instance in which perirenal air insufflation has been done in a patient with a "horseshoe" kidney.

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lowing the intravenous injection of dye, the excretion of contrast medium by the left kidney was satisfactory and there was no deformity of the left kidney pelvis or calyceal system. There was no excretion of contrast medium by the right kidney and the gas shadow remained as aforementioned (fig. 1, A).

TABLE 1. *Gas bacillus infections of the kidney: Reported*

REPORTED BY	YEAR	DIAGNOSIS	OPERATION
Goebel	1895		Autopsy: associated with chronic pyelonephritis
Williams	1896	Urethral stricture with acute urinary retention	Autopsy: associated with suppurative pyelitis
Kelly-MacCallum	1898	Pyonephrosis	Nephrectomy
Howard	1900	Cystitis, orchitis and nephritis	Autopsy: associated with pyelonephritis and chronic interstitial cystitis
Boering	1907	Pyonephrosis	Nephrectomy
Weintrob-Messeloff	1927	Renal tumor	Nephrectomy-sarcoma
Ferrier-Bliss	1928	Renal calculus	Nephrotomy
Knapper	1929	Calculous pyonephrosis	Nephrectomy
Howald	1930	Tuberculous pyonephrosis	Nephrectomy
Meyer	1932	Calculous pyonephrosis	Nephrectomy
		Calculous pyonephrisos	Nephrectomy
		Renal calculus	Pyelotomy
		Renal calculus	Pyelotomy
		Renal calculus	Pyelotomy
Rathbun	1931	Hydronephrosis of horseshoe kidney	Heminephrectomy of left half
Turner	1934	Renal calculus	Nephrotomy
		Renal calculus and abscess	Nephrectomy
Paris-Harvier	1934	Induced abortion	Sound inserted into bladder
Mencher-Leiter	1938	Renal carcinoma	Left nephrectomy
		Renal calculus	Right pyelotomy and nephrotomy
		Renal tuberculosis and calculi	Nephro-ureterectomy
		Renal tuberculosis	Right nephrectomy
		Renal cysts	Drainage and evacuation of cysts walls
		Renal tuberculosis	Right nephrectomy
		Pyonephrosis	Right nephrectomy
		Calculus in ureter	Pelvic ureterolithotomy
		Calculus in ureter	Ureterolithotomy
Lowsley-Hunt	1941	Renal calculus	Nephrotomy
Mendezabal	1942	Calculous pyonephrosis	Nephrectomy
Kawaichi Barnes	1942	Pyonephrosis	Nephrectomy

At cystoscopy, chronic cystitis was found. A 6F ureteral catheter was inserted 27 cm. up the right ureter and with the catheter indwelling, a supine film was made (fig. 1, *B*). Forty cubic centimeters of cloudy urine and 40 cc of air were aspirated from the right kidney pelvis. Approximately 40 cc skiodan 40 per cent was injected through the catheter without producing pain and a pyelogram was made (fig. 1, *C*).

On October 10, 1950, a right nephrectomy was performed with considerable difficulty. The kidney pelvis was opened and two smears taken for culture. The report was Pyocyaneus.

The gross specimen was a kidney which weighed 180 gm. The cortical surface was considerably distorted by numerous crips and depressions and instead of the usual smooth appearance the entire cortex was finely granular throughout. On opening the specimen severe hydronephrosis was noted. The cortical portion of the kidney was considerably and grossly trabeculated. The thickness of the cortex measured roughly 1 to 3 mm. throughout. The pelvic epithelium was altered in that there were numerous granular areas approximately 1 mm. in diameter with somewhat petechial appearance.

ETIOLOGY AND BACTERIOLOGY

Gas bacillus infection of the kidney is usually due to the activities of the Bacillus aerogenes capsulatus (B. welchii, B. perfringens, B. phlegmonis capsulatus emphysematosae). The Vibrion septique, discovered by Pasteur, and the B. histolyticus are also capable of gas production. Other forms of bacteria found in conjunction with those known to be gas-producing are thought to be secondary factors in the production of the condition in that they may consume the oxygen in the wound area which otherwise would act to prohibit growth of the anerobic organisms.

As aforementioned, the majority of gas bacillus infections followed some type of renal or ureteral surgery. Different observers have shown that the source of contamination, in the cases complicating renal and ureteral surgery, may be:

Skin. Meyer and Spector, in culturing the skin of the inguinal region of 100 urban herniotomy cases, found five positive cultures of B. welchii before and two positive cultures after surgical preparation of the skin.

Operative materials. Numerous substantial reports (Meleney, Humphreys and Carp) are to be found in the literature of anerobic infections due to contaminated catgut. It is apparent that the use of such contaminated materials may be another means of introducing anerobic organisms into the wound.

Rectum. It is well known (Tenbroeck and Bauer) that both B. tetani and B. aerogenes capsulatus may be harbored normally in the lower intestinal tract, the incidence being higher in the rural population. Stahr demonstrated by microscopic and injection studies the connection between the lymphatics of the capsule of the kidney with the renal parenchyma and pelvis. Franck demonstrated that in about 20 per cent of the cases he studied the lymph channels of the right kidney capsule are intimately related to the appendix and cecum. He believes that this lymphatic arrangement is occasionally responsible for the migration of organisms from the right colon to the right kidney. Hutchinson believes that bacteria may pass from the bowel to the kidney by way of the lymphatics when lesions of the bowel are present. He cites a case in which an appendix was adherent to the kidney and B. coli were found in the urine.

Mario Fortunato carried out animal experiments which tended to show that the kidney is usually highly resistant to invasion by B. aerogenes capsulatus, and it is only when the organ has been traumatized, or its integrity destroyed by disease, that the infection can gain a foothold. The question arises therefore, as to whether during the mobilization of the kidney and ureter we may not open lymphatics from the bowel in the stripping away of the peritoneum and thus allow organisms to enter the traumatized retroperitoneal area.

Urine, pus and urinary calculi. Mencher and Leiter reported that in a series of 1000 cultures from the genito-urinary tract made at Mount Sinai Hospital, B. welchii was recovered from the urine in 2 cases. Albarran and Cottet stated that in rare cases cystitis may be induced by anerobic bacteria alone or in combination with aerobic organisms. Duvoir et al. mention a case of [illegible] with cystitis that followed the introduction of a sound into the bladder in attempted abortion. Bennett noted the abundant presence of B. welchii in the urine of a patient whose kidney had been traumatized by a proje[illegible]

into the depths for continuous irrigation with peroxide and oxygen. Large quantities of polyvalent perfringens serum are administered intramuscularly, locally and even intravenously. The patient should be isolated and given individual nursing care. Supportive treatment in the form of blood transfusions, infusions, stimulants, etc. is given as required. When the infection subsides, Dakin solution may be alternated with the peroxide irrigations to hasten the separation of necrotic tissue to stimulate granulation of the wound.

All of the gas forming anerobes are sensitive to sulfonamides in vitro (Reed et al.) and *the sulfonamides have proven to be of value clinically.* Penicillin appears to be more effective, however (Hac). Streptomycin is of no value. Chloromycetin, aureomycin and terramycin may prove to be of value after further investigative study.

There is much evidence that combined chemotherapy and antitoxin therapy is superior to either alone (Siebenmann and Plummer). It should be emphasized that chemotherapy is not a cure for gas forming bacillus infections but at best only a supplement to antitoxic and surgical treatment.

Kelly and Dowell, and Williams and Hartzell advocate x-ray therapy for gas bacillus infections. It may be of value, and especially if combined with the aforementioned measures.

Although the prognosis is somewhat better than in the past, it is always grave. Such infections are usually very severe and prostrating and the chances *of recovery are directly dependent upon early recognition* and institution of proper treatment.

SUMMARY

A case of silent intrarenal gas bacillus infection with destruction of the kidney complicating a vaginal ureterolithotomy performed twelve years previously is presented. It is regrettable that the gas forming bacillus was not isolated.

The intrarenal gas shadow is vividly demonstrated by x-ray studies.

A review of the literature was made. The majority of gas bacillus infections of the kidney complicated either renal or ureteral surgery. Thirty cases have been reported prior to report of the present case.

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RENAL PAPILLARY NECROSIS: CASE REPORT

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Although this condition was first described by Friedreich[1] in 1877, it is only during the past 13 years that definite attempts have been made to separate this disease from pyelonephritis as a distinct clinical entity. Numerous theories as to pathogenesis have been suggested, although none, at the present time, is entirely logical.

In 1937, Gunther[2] made an extensive survey of the disease and stressed the association with diabetes mellitus and urinary obstruction and infection. He definitely and conclusively associated diabetes as part of this disease to his own satisfaction.

In 1942, Harrison and Bailey[3] demonstrated that 50 per cent of diabetics had asymptomatic urinary tract infection. In 1944, Robbins and Tucker[4] reported from the Mallory Institute of Pathology, 307 autopsied cases. The cause of death in 6.7 per cent of diabetic patients was pyelonephritis, and most of this group had necrotizing papillitis. In 1946, Robbins, Mallory, and Kinney[5] reported 26 more cases from the Mallory Institute of Pathology, Boston City Hospital, and the Peter Bent Brigham Hospital. Nineteen were in diabetics, and seven were in nondiabetics. Evidence of urinary tract obstruction was not found in the diabetics usually, but the nondiabetics always exhibited evidence of chronic obstruction. The degree or duration of the diabetes was no factor in the pathogenesis. The nondiabetics were in men between 61 and 71 years of age. The acute fulminating cases created the most perplexing problems, and many divergent diagnoses were expressed. The authors believed that the necrotizing papillitis was simply a form of acute pyelonephritis; the pathogenesis being the coalescence of small abscesses at the base of the pyramids with distal ischemic infarction. In 1947, Edmonston, Martin, and Evans[6] reviewed the literature once again and reported on 27 cases, proven by autopsy. Here, too, the same pathological lesions were stressed and the same clinical differentiations reported.

In 1949, Robbins and Angrist[7] reported 14 cases, autopsied at the Queens General Hospital. They classified the disease clinically as acute or subacute. The acute cases occur usually in diabetics with the sudden onset of coma, either with or without acidosis, and generally with azotemia. Pyuria, hematuria, high fever, and leukocytosis were found. The course was rapid and fatal in a few days. The subacute cases were found in:

a) Diabetics with pyelonephritis for a few weeks, and who suddenly became worse.

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bound. The right Murphy sign was 2 plus. Reflexes were physiological. Temperature was 99F rectally.

A diagnosis of right ureteral obstruction, probably calculus, was made, and the patient was referred to the urological department. Urinalysis, cystoscopy, pyelography, both excretory and retrograde, revealed no unusual features. Three hours following the cystoscopic examination, the patient became feverish. His temperature was 104F and his pulse became very rapid. He did not pass any urine during the next 18 hours, and a repeat cystoscopy was performed at 1 a.m. on September 17, 1949. At this examination a large blood clot was seen protruding from the left ureter and no urine could be obtained from the right ureter. The clot was removed and the patient began to excrete urine again. A blood count on admission revealed a leukocytosis of 13,350 with 75 per cent polymorphonuclears and 25 per cent lymphocytes, 4.5 million red blood cells and 15 gm. hemoglobin. Following the episode of acute renal suppression, the urea nitrogen was 50 mg. per cent and the nonprotein nitrogen 100 mg. per cent. The blood sugar was 112 mg. per cent.

Since the fever did not abate and the symptoms of anuria persisted, another cystoscopic examination was performed and indwelling ureteral catheters inserted. The day following this procedure, the urea nitrogen dropped to 23 mg. per cent.

Although the urine was now draining adequately, the patient appeared worse. His face was flushed and pinched. He kept complaining constantly of right abdominal pains. He was now vomiting and had a persistent diarrhea. There was definite right abdominal tenderness and spasticity with a positive rebound phenomenon. Another urologist who was consulted thought that the patient had some intra-abdominal disease. A medical consultant concurred in this opinion, and stated that the trouble was not in the kidneys.

On September 23, 1949, one week after admission, a blood culture was positive for B. coli. A urine culture was also positive for B. coli. The patient had become jaundiced and coarse rales were present at both lung bases. The abdomen was still tender on the right side with persistent peritoneal rebound. A chest film was interpreted as within normal limits. Surgical consultation advised waiting and the continued use of penicillin, streptomycin and aureomycin therapy. The patient improved and the jaundice subsided and repeated blood cultures were negative. Patient was given intravenous fluids and protein, and blood transfusions. The pain in the right abdomen persisted with peritoneal rebound, in spite of the marked general improvement. The temperature remained elevated and continued to spike. An exploratory laparotomy was done on September 28, 1949. No evidence of any intra-abdominal disease was found. A needle biopsy of the right kidney was reported as negative.

Following the operation the patient seemed to improve. But on October 3, 1949, he suddenly became irrational; he responded to orders but appeared quite detached from his surroundings. The left pupil was smaller than the right but reacted well to light. The swallowing mechanism was disturbed. Definite neck rigidity was present. The heart was rapid with a loud systolic murmur at

The remainder of the findings consisted of multiple miliary abscesses of the lungs.

COMMENT

The primary function of any medical scientific investigation is the separation and classification of clinical and pathological entities. However, it will be observed in reading the literature that there is a definite reluctance in regarding papillary necrosis as a specific disease. The tendency is to imply that the distinctive and peculiar alteration in structure encountered in this condition is a form or progression of pyelonephritis. The basis of this hesitancy is produced by the fact that the lesion produced in these cases is not consistent with our present knowledge of the anatomic structure of the kidney. In essence we find multiple areas of ischemic infarction, limited to the conical renal pyramids, surrounded by a zone of leukocytic reaction. This type of alteration in structure is one of the oldest described patterns in pathological anatomy. The pathogenesis of this state has been attributed to vascular occlusion, either mechanical or spastic, supplying the affected area. The difficulty, at present, consists in our inability to demonstrate any vascular system whose sole and only function is to supply the pyramids and the occlusion of which would result in the observed lesion.

The view advanced by Robbins, Mallory and Kinney[5] is that small abscesses form at the corticomedullary junction which by coalescence result in vascular obstruction and subsequent infarction. It would, however, be most difficult to explain by what route the bacteria reached this selective site of localization, and were limited practically exclusively to this site. Certainly neither septicemia nor ascending pyelonephritis can be suggested as an adequate explanation, since neither of these processes involve this area exclusively. Furthermore it could be reasonably expected that at least in some instances the early stages of such a process could be demonstrated.

Robbins and Angrist[7] commented that the pathogenesis is related to the abnormal fat metabolism. That such abnormal chemical physiology exists in diabetics is not disputed. However it must be kept in mind that many abnormal chemical changes in diabetics exist, for example, a marked increase of glycogen in the renal tubules. The simultaneous occurrence of multiple abnormalities does not necessarily indicate that there is a causal relationship.

Furthermore it has been clearly demonstrated that the condition is not related to the duration or severity of the diabetes.[5] It is, of course, apparent that in the considerable group of cases not associated with diabetes, the concept would be entirely inapplicable. Our criticism of this postulation is not to be construed as denying a relationship between diabetes and papillary necrosis, but as suggesting that this relationship is at present obscure and not an essential factor.

The third explanation offered is based on the mechanism of either acute or chronic urinary obstruction. The arguments in support of this theory are based on experimental lesions produced in dogs by ureteral ligation.[9] The deductions drawn from such experimentation must be applied to human material with great caution as must the results of all animal experimentation. The [illegible]

bilateral cortical necrosis are limited almost entirely to tissue derived from the nephrogenic tissue, while others such as papillary necrosis are limited to the structures derived from the metanephros.

Many other renal lesions show a peculiar limitation of distribution, not readily explained, such as glomerular nephritis and nephrosis. The observation that there is some overlapping of lesions is not inconsistent with the hypothesis of different function and response of these separately derived segments of tissue which on fusion form the kidney organ.

It is apparent by analogy to such organs as the adrenal and pancreas, which are composed of tissues of totally different origin and function, that an infectious process, which involves one portion of the structure will by progression affect contiguous areas.

It is also possible, in so far as the kidney is concerned, to demonstrate its dual character by experimental methods. The intraperitoneal injections of adrenalin results in spasm of the cortical vessels, the medullary vessels being uninvolved.[11] In the experimental investigations of the Schwartzman reaction by protein injections, the production of bilateral cortical necrosis is one of the most constant and distinctive features.[12]

It is our belief that this different approach may serve to lead us to a clearer understanding of both the pathogenesis and pathology of renal disease. Although the case we have presented is unusual in many respects, these very features should act as a test of the validity of our previous assumption.

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[12] Schwartzman, G.: J. Mt. Sinai Hosp., **16:** 207, 1949.

duodenal ulcer found. The patient is receiving treatment for this lesion at the present time.

The past history of the patient is tedious but interesting. She was first admitted to the St. Phillip's Hospital at the age of ten and an appendectomy performed. Three years later she was admitted because of a threatened abortion.

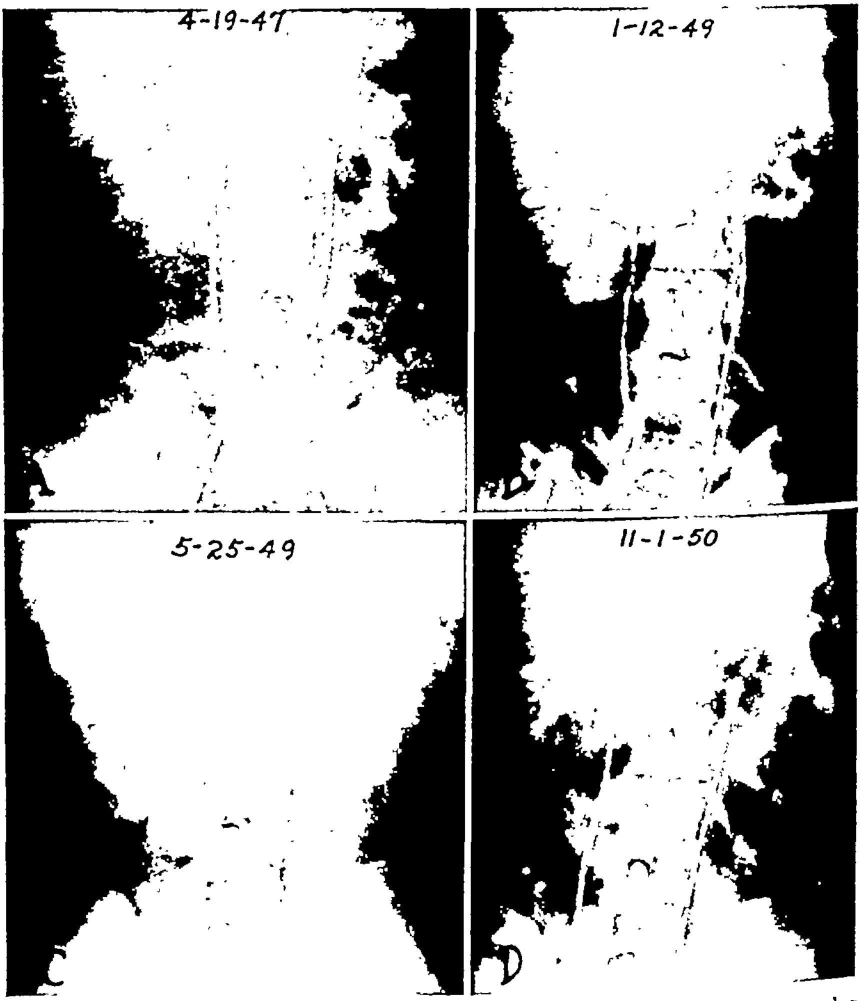

FIG. 1. *A*, original retrograde pyelogram showing multiplicity of calyces. Irregularity at right upper pole is readily noted. Small opacity over rib is a screen defect. *B*, film taken 2 years later. Abscess of upper pole suspected but urine became negative under [illegible] *C*, 4 months later, note rapid growth of cyst. *D*, 5 months postoperative.

At this time there were 2–3 white blood cells per high powered field in the urine. Four months later she was delivered spontaneously of a normal baby. At [illegible] there was an occasional white blood cell in the urine. Two years later she was again admitted because of a threatened abortion. This time there were [illegible] white blood cells per high powered field. She returned in 2 months with the [illegible]

during its growth seems to spread apart two branches of an upper calyx which should represent the entire calyceal system for that portion of the kidney. Unfortunately, no films were made during her first attack of pyelonephritis which occurred during the puerperium and we are unable to state positively that a minor calyx was not sealed off at that time. Again, however, we believe that the evidence is against this possibility. This leaves us then with the diagnosis of infected simple or serous cyst, a rare lesion, which according to Abeshouse has been reported in only 5 cases. The question arises as to how the cyst became infected. Our theory is that during the puerperium back pressure was exerted against the calyceal system. Infection supervened and bacteria made their way across the tissue barrier of the capsule into the lumen of the cyst. In the same manner, after the assumed dilatation of the right renal collecting system had subsided after puerperium, intracellular fluid flow was away from rather than toward the now infected cyst and bacteria again made their way across the tissue barrier into the collecting system and an exacerbation of pyelonephritis was produced. This would account for the prompt clearing of the urine by the use of antibiotics and equally prompt recurrences.

The final question as to why the cyst should increase in size more in 3 weeks than in the previous 2 years remains unanswered even in theory. We can merely say that it occurred and has been reported previously in other cases.

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Parasites escaping these hazards, pierce the stomach mucosa or upper intestinal tract, filter into the portal circulation and usually become embedded in the liver. A small number bypass the portal circulation and enter the lungs. Some few escape the pulmonary venous plexus, become dispersed and finally arrested in various body tissues. Approximately 77 per cent of cysts form in the liver and about 10 per cent in the lungs. The remaining 13 per cent are deposited in other portions of the body. About 2.5 per cent reach the kidney; here the embryo embeds itself in cortical tissue and within a few hours forms a small blister-like cyst and in years attains mature size.

At maturity, the cyst is composed of an adventitious capsule inside of which is a laminated nutritive layer lined by a germinal membrane. From this endocystal germinal membrane, brood capsules develop. At least part of the cyst surface is covered by renal capsule.

The cyst has no blood supply. Nutrition is supplied by selective osmosis through the laminated covering. This layer is impervious to noxious substances and for this reason destructive medications cannot reach the interior.

As the original hydatid enlarges, it reproduces within itself daughter cysts whose construction is a replica of the parent. The mother cyst wall expands to accommodate the multiplication of offspring and the increased amount of nutritive fluid. While it grows, the mass encroaches on the pelvis and parenchymal renal tissue obliterating some of its blood supply and destroying function. As a result of pressure necrosis, rupture into the renal pelvis can occur and cyst contents expelled into the urinary tract. In such an event, microscopic examination of the urine will show fragments of cyst wall, scolices, hooklets. Invariably, following this outcome, infection develops, involving the renal pelvis and surgical treatment of urosepsis becomes necessary.

On the other hand, if pressure is exerted on the peritoneal side with resultant rupture, the contents are expelled intraperitoneally. Following such a complication, the patient experiences abdominal distress and severe anaphylactic shock. The host is sensitized to the cyst fluid and the shock may be severe enough to cause death.

The contents may gravitate down to the pelvis and start new areas. If a new cyst forms in the retrovesical space, it may occasion bladder neck obstruction requiring operation.

In about 20 per cent, the wall undergoes calcification preventing the entrance of nutritive substances and degeneration results. A pathologic picture simulating tuberculous caseation follows. In such a termination, the cyst becomes an innocuous mass, which does not trouble the host and usually requires no treatment.

SYMPTOMATOLOGY

Twenty to thirty years of development are required for the cyst to cause symptoms. The growth acts as a foreign body and causes distress by pressure. The patient complains of flank discomfort and may also note a mass in the [illegible]. If the cyst ruptures into the pelvis of the kidney, colicy pains are experienced when the small daughter cysts pass down the ureter.

The anaphylactic reaction following rupture into the peritoneum has already been mentioned. Ordinarily, the unruptured, modest sized cyst is asymptomatic. The patient's nutrition is normal and his health is not obviously interfered with.

DIAGNOSIS

In countries where the disease is prevalent, the diagnosis is frequently made preoperatively because it is always suspected, but in the United States, since so few cases are encountered, it is rarely detected until after exploratory operation. Preoperative diagnosis was made in only four of 17 cases reviewed by Kretschmer.

[illegible]

signs could be considered definitive. Intradermal tests and compliment fixation studies have been developed to aid in detecting the presence of the disease.

PROGNOSIS

If untreated, it may end fatally. About 20 per cent develop calcification of the cyst wall with autodestruction of contents. In most instances, the involved kidney is sacrificed. In some cases, the hydatid has been successfully resected from renal tissue.

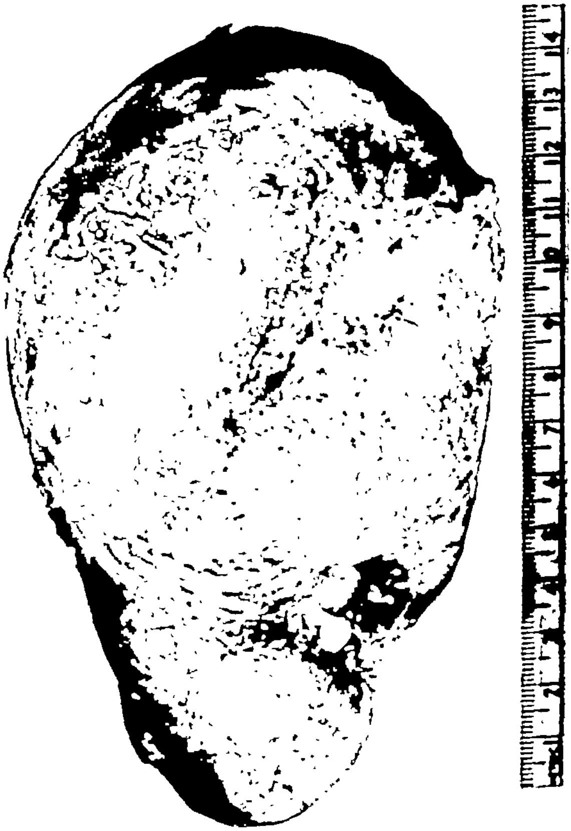

Fig. 2 Gross specimen

TREATMENT

Nephrectomy appears essential. Because the laminated membranes are impervious, therapeutic medication is of no value. Marsupialization and treatment with formaldehyde are advocated by some. If the patient has no other organs involved, nephrectomy results in a cure. Dew claims that 60 per cent of patients have multiple cysts. Bilateral renal involvement is rare.

PROPHYLAXIS

It had been predicted that the disease will become more prevalent in this country with increase in sheep raising, however, this has not occurred. It [illegible] of our enlarged, wool-growing industry the disease remains rare. On the other hand, it has become less frequent in those countries adopting modern American [illegible] supervision of abbatoirs.

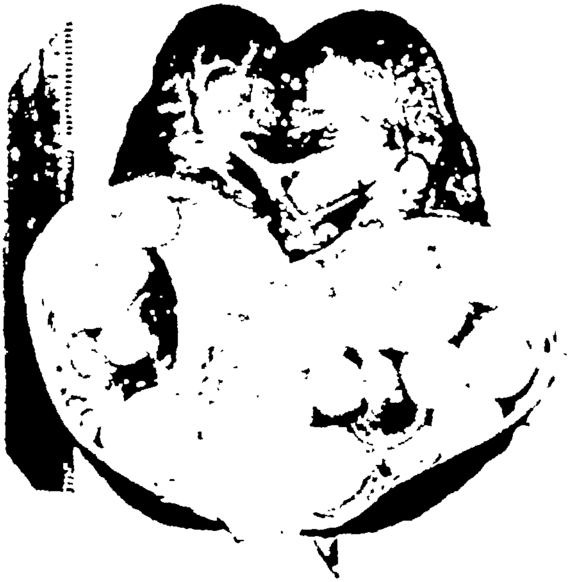

Fig. 3. Cyst opened showing daughter cysts.

had gone through two pregnancies during the preceding three years without unusual difficulty.

Until her marriage, she was never outside of her native country. Her parents were chicken raisers in a wool-growing country district. As far back as she could recall, a pet dog was always around the home. She had no knowledge of the prevalence of echinococcus disease in her native community. Her parents, brothers and sisters were all living and well.

Cardiorespiratory and gastro-intestinal system studies showed nothing remarkable. In the right renal area, a regular, slightly tender, rounded mass was easily palpated. The upper border extended above the costal margin.

Excretory urography showed a normal pyelogram on the left side but no dye was excreted on the right after 1 hour. The enlarged kidney shadow was distinct and appeared to be about three times normal size. Retrograde study showed an extreme degree of compression deformity on the involved side. Specimens of urine were negative on microscopic examination. Indigo carmine appeared within normal time limits from the left but only a faint trace after a prolonged time was obtained from the right side. Exploratory operation with possible nephrectomy was recommended and the patient submitted.

The kidney was approached through a flank incision. Mobilization was rather difficult because of adhesions. Rough handling of the mass on the lower pole did not result in rupture. The mass was firm yellowish in color, and fluctuation was not observed. Our diagnosis was hypernephroma and nephrectomy was performed. The specimen was about three times the size of a normal kidney. About one-fourth was renal tissue and the rest was the attached mass (fig. 2). The incision was treated in the usual manner and closed without drain. On section, the thick capsule of the mass retracted and numerous spherical cysts rolled out (fig. 3). They varied from the size of a match head to that of a pigeon's egg (fig. 3). Dozens of these were enclosed in the large mother cyst and were surrounded by a colorless fluid. These were the daughter cysts in various stages of development. They were filled with a clear fluid and were a miniature replica of the larger cyst. The renal tissue was compressed and distorted by the attached mass. On microscopic section (fig. 4) numerous hooklets, brood capsules and scolices were identified.

The patient made an uneventful recovery and no evidence was found of any other cysts.

CONCLUSION

Echinococcus disease is rare in the United States. The kidney is involved in about 2.5 per cent of instances. The life cycle of the parasite is described. The symptomatology, pathology and treatment as reported by foreign writers are reviewed. An uncomplicated case treated by nephrectomy is presented.

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Excretory urograms showed a functionless left kidney and a normal right kidney. The retrograde pyelograms demonstrated a moderate dilatation of the internal structure of the left kidney, a slightly dilated upper ureter without filling of the lower portion, and a normal right kidney. The roentgenogram of the thoracic and lumbar portions of the vertebral column revealed hypertrophic arthritis in the lower lumbar vertebrae. The roentgenograms of the gastro-intestinal tract and the colon after administration of barium were normal.

On August 15, 1949 the patient was found not to have passed urine since the previous evening. At the time of cystoscopy on August 15, only 2 to 3 cc of blood-tinged urine were evacuated from the bladder. Ureteral catheters were passed bilaterally. Some obstruction to the catheters was encountered at about 5 cm. but this was overcome. About 50 cc clear urine was obtained from each pelvis.

It was apparent that a bilateral ureteral obstruction from an external cause of unknown etiology was present. The most likely diagnosis was that of a retroperitoneal neoplasm.

At the time of exploratory laparotomy on August 16, 1949, a firm, slightly hemorrhagic mass extending from the kidneys down over the sacrum and measuring about 15 by 8 cm. was found in the retroperitoneal area. The ureters were imbedded in the mass and were not dissected free. A small piece of the tumor was removed for biopsy.

A moderate elevation of temperature which gradually subsided was present for about 10 days postoperatively. The ureteral catheters were removed on August 29, 1949. The patient voided thereafter. The value for the nonprotein nitrogen rose to 116 mg. per cent on August 31, and gradually dropped to 39.5 mg. per cent by September 23.

Biopsy from the retroperitoneal area revealed a subacute inflammation. Numerous lymphocytes, plasma cells and polymorphonuclear neutrophilic leukocytes were found in areas of granulation tissue and scar. Small abscesses were scattered throughout the tissue. Evidence of neoplasm was not present.

Serum agglutinations for the typhoid, paratyphoid, salmonella, brucella, tularemia and typhus organisms were normal. *Pseudomonas aeruginosa* and *Aerobacter aerogenes* were isolated from the urine.

Aqueous crystalline procaine penicillin G, 50,000 units were given intramuscularly every 3 hours from August 15 to September 23. Because of the *Aerobacter aerogenes* in the urine, 0.05 gm. of the antibiotic Q-19* in 1 cc of physiologic saline was given intramuscularly every four hours from September 23 through October 7, 1949. The response to treatment was excellent. At the time of discharge on December 23, 1949, the patient, although underweight, felt well and was voiding normal quantities of urine freely.

The patient re-entered the hospital for further study on April 3, 1950. He felt well and had gained 47 pounds in weight. The value for the nonprotein nitrogen was 50 mg. per cent on April 4, and 37 on April 12. Urinalysis showed a mild degree of albumin, numerous leukocytes and rare erythrocytes. *Pseudomonas aeruginosa* was isolated from the urine. Excretory urograms showed a mod

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* Supplied by Upjohn and Co., Kalamazoo, Mich.

led to a diagnosis of renal insufficiency with uremia. Excretory and retrograde pyelograms showed a bilateral hydronephrosis. A bilateral nephrostomy was done on September 28. The postoperative course was uneventful. In the following months, definite improvement was reflected in the general condition and in laboratory investigations. Re-examination on April 21, 1947 showed a good general condition, an increase in weight and an improvement in the degree of anemia, leukopenia and eosinophilia. A right nephrectomy was done on April 29. In October 1947, the left ureter was freed of adhesions and the nephrostomy abolished. The patient made a satisfactory recovery and has done well.

Case 4.[3] A 41 year old white man was first seen on December 4, 1948 because of oliguria and uremia. The value for the urea nitrogen was 284 mg. per cent, the creatinine 14.2 mg. per cent and the carbon-dioxide combining power 29 volumes per cent. Obstruction was not noted in the course of the ureters and the retrograde pyelograms were not remarkable. The urine obtained from the kidneys was sterile. With the ureteral catheters in place, a return to normal of the previously mentioned constituents was noted. After removal of the catheters, oliguria and azotemia recurred. Exploration of the right kidney was done and the kidney was found constricted by indurated adipose tissue. The fat was freed from the kidney and biopsy of the adipose tissue showed a severe inflammation. Shortly after the time of surgery, the values for the various constituents returned to normal. Due to the fact that the patient made a good recovery, the left side was not explored. Retrograde pyelograms made several months later showed normal function of both kidneys without evidence of disease.

Case 5.[4] A 49 year old white man was seen first on December 19, 1949 for a dull, aching pain in the left upper quadrant of the abdomen and the left renal area. The illness became acute 7 weeks previous to admission with symptoms and signs suggesting a typical left renal ureteral colic. At the time of admission, the value for the nonprotein nitrogen was 41 mg. per cent. Excretory urograms did not show function on the left over a period of 3 hours but the right side was normal. At the time of cystoscopy, catheters were easily passed up both ureters. Retrograde pyelograms showed a moderate dilatation of the pelvis and major and minor calyces of the left kidney. Culture of the urine obtained from the left kidney at the time of subsequent cystoscopy showed Staphylococcus albus. Culture of the urine for the tubercle bacillus was negative. Left nephrectomy was advised and subsequently accomplished. Considerable thickening of Gerota's fascia and marked edema and fibrosis of the perirenal fat were found. An acute and chronic pyelonephritis was reported to be present by the pathologist. The patient was seen again on April 7 when he was in good condition. On April 14 the patient returned because of constant nausea and painless anuria for about 18 hours. At the time of cystoscopy a catheter was passed up the right ureter and about 70 cc clear urine was removed. Retrograde pyelogram showed a dilatation of the

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[3] Helfert, I. Personal communication.

[4] Lovell, George H. Personal communication.

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PERI-URETERAL AND PERIPELVIC (RENAL) EXTENSION OF CARCINOMA OF CERVIX: CASE REPORT

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The urological complications of carcinoma of the cervix have been extensively reported: lower ureteral obstruction with hydronephrosis, pyonephrosis, and terminal uremia is a familiar one. We wish to report an unusual type of peri-ureteral and peripelvic (renal) extension, which, it is believed, may be of significance in the problem of lymphatic drainage from pelvic organs to renal pelvis.

CASE REPORT

M. P., a 45 year old Greek woman (multipara), was admitted to the Jewish Hospital of Brooklyn, February 20, 1949, with a 36 hour history of lower abdominal pain. A fungating lesion at the cervical os and palpable masses in each adnexal region were found. Histopathological examination of biopsy specimen from cervix and cell smear led to a diagnosis of epidermoid carcinoma (fig. 1, *A*). Urograms, urinalysis, and blood urea were normal. The patient was discharged on March 7, 1949 and referred to the outpatient department for deep roentgen therapy.

On April 11, 1949, the patient was re-admitted because of constant pain and persistence of abdominal masses. No evidence of a cervical lesion, described before therapy, was found; the urine, chest and colon studies were normal. Because a dysgerminoma was suspected, a total hysterectomy, bilateral salpingo-ophorectomy and dissection of pelvic lymph nodes was performed. The gross findings at operation did not suggest extension of malignancy. The pathologist's report (Dr. David Grayzel): 1) uterus with leiomyomas, subserosal; 2) fallopian tube with hydrosalpinx, bilateral; 3) normal ovaries; 4) no involvement of lymph nodes; 5) epidermoid carcinoma of cervix with inflammatory reaction, chronic.

Convalescence was uneventful, and the patient was referred to out-patient department on May 4 for further deep roentgen therapy.

The third admission was January 20, 1950, because of severe pain in right hip and right thigh of 2 months duration. In the opinion of the gynecological consultant, the patient did not have metastatic disease. The neurological consultant suspected a disc, and myelograms demonstrated a persistent filling defect between L4 and L5. Urograms, February 11, 1950, were reported as showing mild pyelectasia, mild calectasia, right, and normal kidney and ureter, left. Urea estimation was normal.

Retrograde studies (fig. 2) confirmed the findings on the right and revealed, in addition, a normal bladder and an easily passable obstruction in the right ureter at 6 cm. and 18 cm. Urine from bladder and right kidney was negative. A large herniated disc was removed February 16. Persistence of pain and onset of febrile course, however, dictated a repeat urological investigation. Excretory urograms, March 1, revealed a nonfunctioning right kidney. Retrograde studies showed a marked increase in calectasia, and an impassable obstruction at 15 cm.

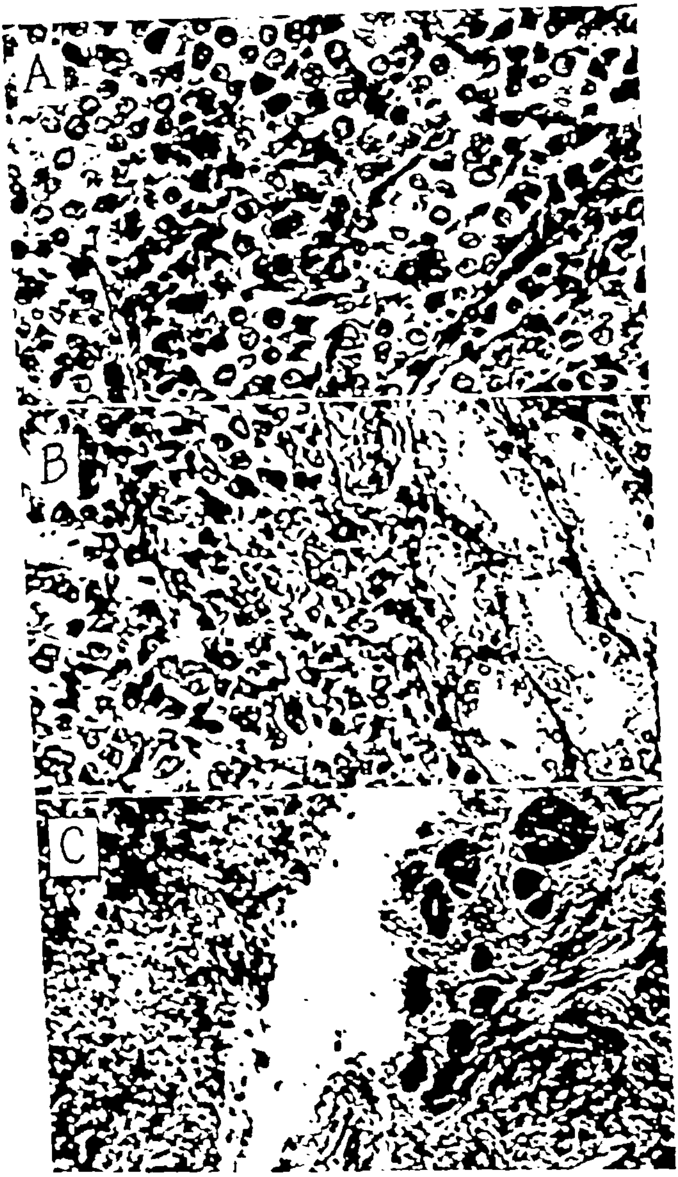

FIG. 1. *A*, carcinoma of cervix. *B*, metastatic carcinoma to kidney. *C*, metastatic carcinoma, peri-ureteral. H & E, ×350.

Urine from the bladder was negative on culture; that from the right renal pelvis gave positive cultures for B. pyocyaneus. Lack of response to antibiotics and persistence of pain led to nephrectomy and partial ureterectomy (right) March 20, 1950.

OPERATIVE FINDINGS

The kidney was swollen about 2 times normal size, firm, tense and slightly cyanotic. Completely enveloping the renal pelvis was a hard, nodular, greyish-white mass about 7 cm. in diameter, discrete from but bound to the adjoining tissue. At the hilus, this mass insinuated itself between pelvic and cortical tissue. The lower pole of the kidney was loosely fixed to the upper portion of the ureter. The renal vein was not grossly involved.

The ureter was thickened to 1½ cm. in superior portion and enveloped, as was pelvis, by hard, nodular, defined tissue. This nodular infiltration extended inferiorly as far as could be palpated (below pelvic brim), but in its inferior portion, it was thought to be less indurated. Tissue medial and lateral to the indurated ureter was not grossly involved. After removal of a portion of the ureter, multiple small nodules could be palpated in its bed. Some purulent drainage from the open end of the ureter was noted. The peritoneum peeled easily from Gerota's fascia and was not grossly involved.

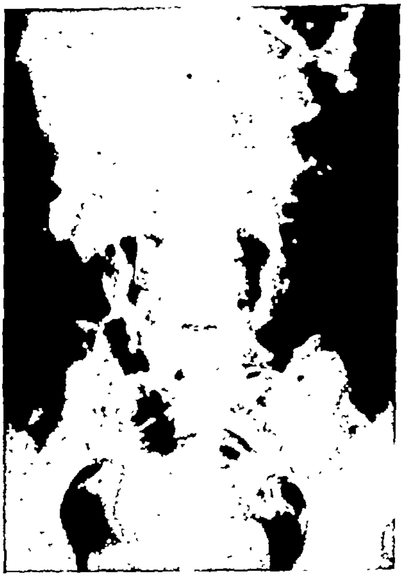

FIG. 2. Right pyelo-ureterogram demonstrating pyelectasis, calectasia and dilated ureter, right.

Pathological report (Dr. Grayzel): "The kidney weighed 248 gm.; the capsule stripped with ease, revealing a pale, scarred and smooth surface. In one area, there is an irregular, hard flat, grey-white nodule measuring 1 cm.

"Surrounding the hilar region and the 4 cm. of attached ureter is a confluent mass of grey-white lobular tissue measuring 8 by 5 by 3 cm. On cut section, this tissue is seen to invade about the pelvis and calyces. The mucosa of the pelvis and calyces is invaded and replaced by tissue in areas. The cortex and medulla are poorly differentiated and measure 0.5 and 1 cm. respectively.

"The portion of attached ureter is involved by tumor tissue thickening the wall to 0.35 cm. in areas. The mucosa is replaced by tumor. Accompanying the specimen is a 2 cm. portion of the ureter. The external surface is pink-grey and the wall is thickened to 2 cm. The mucosa is grey, smooth and glistening.

"Microscopic: (fig. 1, *B* and *C*): The tumor consists of cylindrical and polygonal cells varying in size, shape and nuclear staining. Mitosis is numerous. The cells are arranged in alveolar formation.

"Diagnosis: Kidney with portions of ureter, right, with metastatic carcinoma, peripelvic, and peri-ureteral, and with chronic and acute suppurative pyelonephritis, and with infarct in kidney."

DISCUSSION

We have considered peri-ureteral and peripelvic (renal) vertical extension of carcinoma of the cervix as uncommon and a fairly extensive review of the literature has confirmed our impression. The mode of spread of carcinoma of the cervix is described by numerous authors but neither in text nor in papers reviewed,[1] have we encountered a similar description. Katzen,[2] in fact, states: "Thus, in late carcinoma of the cervix with invasion of the broad ligaments and retroperitoneal lymph nodes, obstruction of the upper ureter does not occur. The familiar terminal picture is rather the result of carcinomatous infiltration surrounding and compressing the lower ureter."[3] It is evident, we believe, that this type of extension to the upper ureter, is uncommon if not rare.

Of equal interest is the possible significance of this case in the question of lymphatic pathways from the pelvic organs to renal pelvis and kidney; this question is still subject to discussion and three views are held: 1) that direct vertical transmission from pelvic organs to renal pelvis and kidney by way of lymphatics occurs;[4] 2) that direct vertical transmission via lymphatics is improbable because of segmental character of ureteral lymph drainage;[5] 3) that spread occurs lymphohematogenously, i.e. regional lymphatics to thoracic duct to general circulation, thence to kidney.[6]

A fourth view, that of fascial planes, while not technically lymphatic, is invariably discussed under this problem. As Winsbury White states it . . ."The spread of an inflammatory process from any pelvic organ is shepherded by this fascial sheath (urogenital fascia) towards the kidney."[7]

A virtually solid column of tissue extending along and enveloping the ureter calls to mind vertical transmission from pelvic organs to kidney. A lymphatic pathway is strongly suggested by the positive lymph nodes, the invasion of submucosa and peri-ureteral sheath, so rich in lymphatics, the known predilection of carcinoma of the cervix for lymphatics and the extreme unlikelihood that so extensive an involvement could be completely extralymphatic.[8]

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[1] A total of 568 autopsy studies and surgical removals were covered by papers reviewed, as well as over a thousand clinical reports.

[2] Katzen, P.: J. Urol., 36: 120–1936, 1935.

[3] Possibly pertinent, but not necessarily demonstrating longitudinal extension, is Carson's finding of carcinoma cells in perivascular lymphatics of ureter and renal pelvis secondary to primary carcinoma of bladder, prostate and cervix uteri. (Cited by MacKenzie, D. W. and Wallace, A. B.: J. Urol., 35: 518, 1935.

[4] Rolnick, H. C.: The Practice of Urology. Philadelphia: J. B. Lippincott Co., 1949, vol. 2, p. 729.

[5] MacKenzie, D. W. and Wallace, A. B.: Op. cit. p. 516.

[6] Rolnick, H. C.: Op. cit. vol. 2 p. 730.

[7] Winsbury White H. P. Ed., Text Book of Genito-Urinary Surgery. Livingston of Edinburgh, 1948, p. 713.

[8] Moore points out that the most "significant regional nodes (in spread of carcinoma of cervix) are located where lymph vessels cross ureters at bifurcation of common iliac nodes. p. 1136 R. A. Moore: Text Book of Pathology, 1944.

Similarly, however, the confinement of spread to an actual column speaks for restriction by fascial planes—the so-called "pilaster" described by Thompson[9]

Thus it would appear that there is, in the case described, a clinical example of vertical extension of carcinoma of the cervix to renal pelvis, in all probability by way of lymphatic channels and fascial planes.

Some speculation about factors influencing the type of spread described suggests itself. The voluminous experimental work demonstrating segmental drainage from ureter indicates that vertical transmission is uncommon. Undoubtedly multiple factors operate. MacKenzie and Wallace demonstrated development of collateral lymphatics when some channels were seared. The foreign particles, however, still moved toward aortic nodes. It is a possibility that removal of lymph nodes at previous surgery, in this particular case, might have influenced the route. It is perhaps significant that Rolnick demonstrated vertical transmission in isolated post-mortem specimens of the kidneys, bladder, and ureters.

SUMMARY AND CONCLUSIONS

A case of unilateral peri-ureteral and peripelvic (renal) extension of carcinoma of the cervix is presented. A review of the literature indicates this is a rare type of extension. It is suggested in addition, that the case is a clinical example of vertical transmission via lymphatics and fascial planes of carcinoma from a pelvic organ to renal pelvis.

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[9] Winsbury White H. P. Ed: Op. Cit. p. 11.

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VESICO-URETERAL REFLUX IN THE PARAPLEGIC: CAUSE AND CORRECTION

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The incidence of vesico-ureteral reflux in paraplegic patients is high and its presence is associated with progressive renal damage. As Hutch and Bunts have shown, the incidence of reflux in patients who have been paraplegics for 3 years is 13 per cent and there is a tendency for this percentage to increase even more with the passage of time. Now that the cystogram is becoming a part of the routine checkup examination in paraplegic patients, an even higher incidence may be reported. That reflux is damaging to renal function is illustrated by the fact that of 14 deaths on our paraplegic service due to urologic causes, nine were due to reflux and its complications. In our series of 55 patients with reflux, 17 kidneys required nephrostomies and two skin ureterostomies to preserve their dying function. We also found that renal function, as determined by excretory urography showed only minimal damage during the first 3 years following cord injury in spite of the fact that hydronephrosis and hydro-ureter and calyectasis was present in about 25 per cent of the cases. It was not until after the third year that severe damage to renal function was found and this was associated with a sharp rise in the incidence of vesico-ureteral reflux.

Other urologists have come to regard reflux as a definite danger to the upper urinary tract. Prather states: "Since there is both experimental and clinical evidence that an incompetent valve permits direct ascending infection and if continued over a long period of time produces a hydro-ureter, it behooves us to attempt to remedy this abnormality when found in clinical practice." Wislocki and O'Conor have shown experimentally how this hydro-ureter may be produced as a result of vesico-ureteral reflux. Using rabbits and dogs they filled the bladder with a fluid stained with methylene blue. After the animal was anesthetized, a laparotomy was done so that both ureters could be visualized. They wrote "while the ureters are under direct observation, a column of blue dye suddenly fills the lumen of the right ureter. A peristaltic wave which has already left the renal pelvis meets the column of blue in the upper half of the ureter and impedes its progress. Fresh peristaltic waves commence above, becoming more and more frequent and vigorous and a struggle ensues for the control of the ureter." In some of their experiments the dye was expelled from the ureter; in others, the methylene blue filled the entire ureter and pelvis.

Having thus convinced ourselves that vesico-ureteral reflux occurs in a high incidence in paraplegic patients and that its presence constitutes a grave danger

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Note by editor: Dr Hutch's manuscript was awarded first prize by the Committee on Scientific Research, Dr Miley B. Wesson, chairman.

to the function of the upper urinary tract an effort was made to learn more about this phenomenon.

The intravesical and intramural portion of the ureter is a highly specialized valve. It has for its function the task of permitting urine forced into it by ureteral peristalsis to pass into the bladder and, secondly, to prevent the passage of urine from the bladder into the ureter. When working efficiently, the valve is able to accomplish both functions regardless of the degree of fill of the bladder.

Considerable study has been given to the anatomy of the ureterovesical valve and its insertion into the trigone. While all writers do not agree, there is good evidence to support the belief that the muscular layers of the ureter extend beyond the ureteral orifice and insert into the trigonal muscle. Gruber summarized the work of those who hold this view:

“In 1812 Bell described muscle fibers which he thought originated from the ureters and passed across and downward under the mucosa forming what are known as the lateral boundaries of the trigone. His observations were confirmed by Ellis in 1856. In speaking of Bell's muscle, he says, 'Behind, below, the opening of the ureters, this stratum receives an accession of fleshy fibers from the muscular coat of those tubes.' Søppig in 1874 describes the ureter muscles as dovetailing with the bladder muscle for reinforcement of both the ureter and bladder. In a similar tone Wesson reports: 'The adventitia of the ureter, beginning several centimeters above the bladder, is strengthened and thickened on the dorsal side by robust longitudinal bundles of involuntary muscle that follow the ducts to their vesical ends and in conjunction with the fibrous tissue in which they are imbedded, form Waldeyer's ureteral sheath. From this sheath bands of muscle (Bell's muscle) pass toward the vesical orifice along each side of the trigone while other (Mercier's bar) unite the orifices forming the base of the triangle. These fibers are probably a continuation of the longitudinal muscles of the ureters or of Waldeyer's sheath.” At any rate, the insertion of the ureter into the trigone is firm enough to securely anchor the ureter into a fixed portion of the bladder.

In 1903 Sampson developed the idea of the oblique passage of the ureter through the bladder wall. His article contains excellent microphotographs of the ureterovesical junction with the bladder empty and distended. As the bladder is filled with fluid, the course of the ureter through the bladder becomes more and more oblique. This is made possible by the insertion of the distal tip of the ureter into the fixed trigone while the intravesical and intramural portion of the ureter is carried upward as the detrusor behind it is stretched. Sampson also shows that the lumen of the intravesical portion of the ureter is round when the bladder is empty and flattened or compressed as the bladder is distended. He postulates that it is this compression of the intravesical ureter between a firm bladder wall behind and an increasing pressure in the bladder that prevents reflux. Sampson also shows that the intravesical and intramural ureter pass through the bladder as a separate structure.

Gruber made a comparative study of the trigone and intravesical ureter in rabbits, cats, pigs, dogs and humans. The susceptibility of these species to reflux varies greatly. (As many as 86 per cent of rabbits showed reflux according to

Graves and Davidoff, whereas a normal human bladder practically never allows reflux.) Gruber found that in species which were very susceptible to reflux the trigone was poorly developed and the intravesical ureter was short, whereas in humans and other species where reflux is rare, the trigone is well developed and the intravesical ureter is long. Gruber also showed in a second article that destruction of the intravesical portion of the ureter in humans produced reflux. From fresh human cadavers he removed the bladder along with the lower ureters and part of the urethra. He sutured the urethra tightly. Then, through a small opening in the dome of the bladder he removed the roof of one intravesical ureter leaving the other intact. In eight of nine specimens so treated, distention produced reflux up the damaged ureter. Never did it occur on the undamaged side.

From this brief review of the existing information on the subject one might conclude that the anatomy of the ureterovesical junction in the human is designed to prevent reflux. The ureter is firmly attached to the trigone and there is a long intravesical ureter under which lies a firm detrusor muscle.

A careful study was made of 300 cystograms, 94 of which showed reflux. It was observed that there often occurred an outpouching or a saccule or small diverticulum in the region of the ureterovesical junction. This was noted in 60 of the 94 cystograms which showed reflux. It was occasionally noted on cystograms which did not show reflux. Most paraplegic patients who develop reflux have small, heavily trabeculated bladders and the presence of saccules or small diverticula is to be expected. It was only after seeing many such cystograms that the consistent association of this defect with the ureterovesical junction became apparent. (See figure 1).

Since the cystogram is two dimensional, it is impossible to be certain that any saccule in the bladder is associated with the ureterovesical junction even though this association seems quite definite by cystogram. Therefore, cystoscopic confirmation is necessary to prove or disprove this assumption. Thirty patients with reflux were examined cystoscopically with this point in mind and a definite saccule about the ureteral orifice was demonstrated in fifteen. These saccules had certain characteristics. First, they lay above and lateral to the ureteral orifice. They involved the bladder wall just beyond the lateral points of the trigone but never involved the trigone itself. Second, when a ureteral catheter was passed through the ureteral orifice it would outline the ureter passing under the floor of the saccule (fig. 2, *A* and *B*).

On the basis of the foregoing, it is postulated that a saccule may occur in the region of the intramural ureter. This saccule involves the detrusor muscle which normally lies under the intravesical and intramural ureter and weakens or destroys this muscle. When this happens vesico-ureteral reflux often occurs because there is no longer any firm muscle lying under the intramural ureter. Hence, there is no longer any firm muscle for the ureter to be compressed against as the intravesical pressure increases and reflux may occur.

It was also noted from a study of the cystograms of these paraplegic patients that the contrast medium outlining the ureter would often stop a short distance above the bladder as though the ureter was obstructed just as it entered the

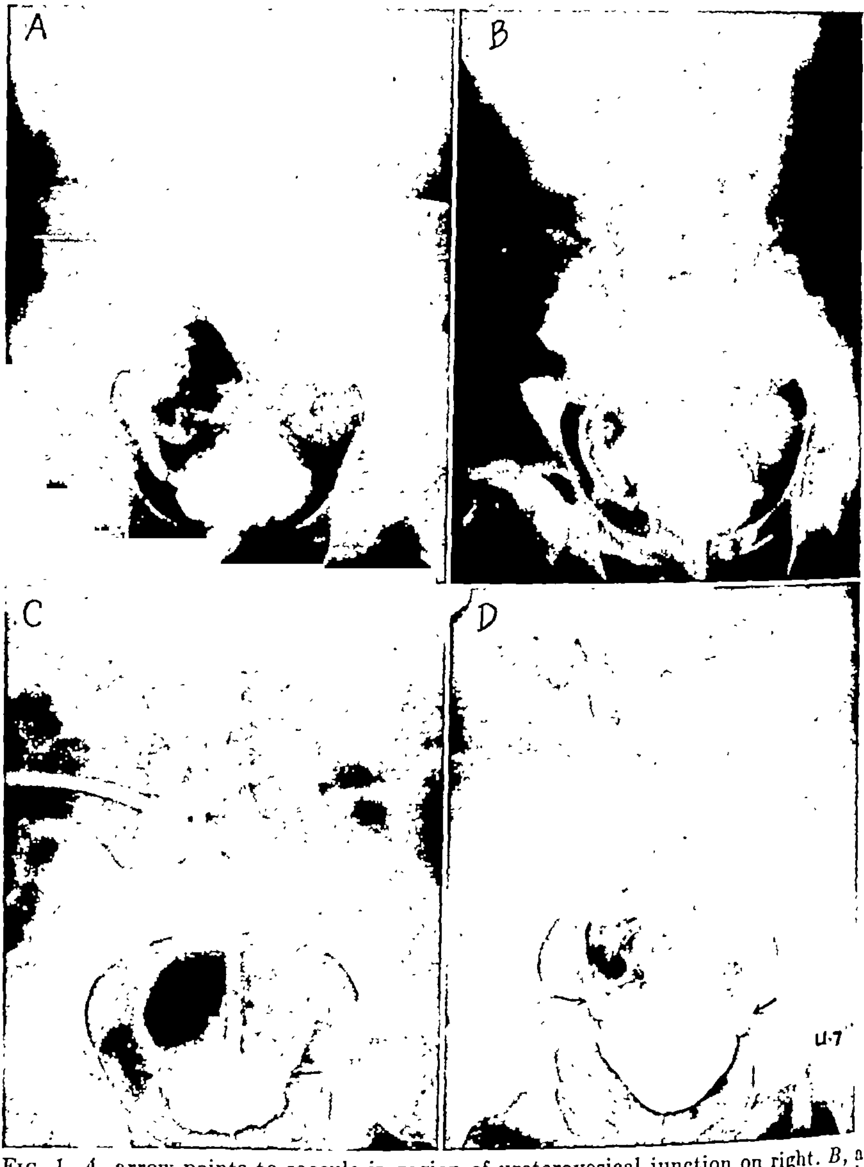

FIG. 1. *A*, arrow points to saccule in region of ureterovesical junction on right. *B*, arrows point to saccules in region of ureterovesical junction bilaterally. *C*, arrows point to saccules in region of ureterovesical junction bilaterally. *D*, arrows point to saccules in region of ureterovesical junction bilaterally. Incidently, defect in ureter referred to in text as the "notch sign" is illustrated in all four cystograms.

bladder. This defect was observed in 57 of the 94 cystograms that showed reflux. At first it was believed that it represented an organic obstruction of the ureter and this was substantiated by the high incidence of hydronephrosis and hydroureter and the delayed emptying of the involved upper urinary tract as observed by excretory urography in these cases. On the other hand, none of these ureters demonstrated any actual decrease in the caliber of its lumen when ureteral catheters were passed into them. (See fig. 1). What the significance of this notch sign may be or what part it plays, if any, on the reflux and hydro-ureter of the paraplegic is not clear at this time.

Based on the assumption that reflux in paraplegics is due to a loss of support of the bladder behind the intravesical and intramural ureter an operation has been designed to correct this condition. There are three main principles involved. First, the ureter must maintain its attachment to the trigone. Second, a long intravesical ureter must be created and third, the bladder behind the intravesical ureter must be repaired (fig. 2, *C*).

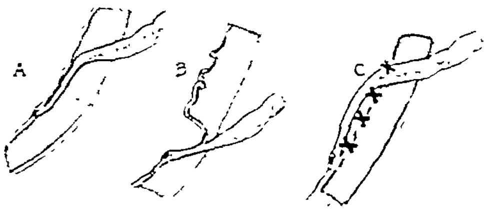

FIG. 2. *A*, course of normal ureter passing through normal bladder. *B*, saccule above ureteral orifice. Note how course of intramural ureter is altered. Saccule must have resulted from weakness of detrusor muscle which normally lies under intramural ureter. *C*, postoperative position of ureter. Attachment at trigone has been preserved. Long, intravesical ureter has been created. Defect in bladder under ureter has been firmly sutured. X marks indicate position of sutures.

OPERATION

Preoperatively a No. 6 polyethylene ureteral catheter is passed cystoscopically and left indwelling in the involved ureter. The patient is then taken to the operating room and given a satisfactory anesthetic. With the patient on his back and the pelvis slightly elevated, a midline suprapubic incision is made between the umbilicus above and the symphysis below. This incision is carried through the superficial fascia and the anterior rectus sheath in the direction of the skin incision. The rectus muscle is then separated in the direction of the skin incision, exposing the bladder below and the peritoneum above. The peritoneum is reflected upward from the anterior surface of the bladder and medially from the lateral abdominal wall. Thus, the lower portion of the involved ureter is exposed. The ureter is then dissected downward until it can be seen disappearing into the bladder wall. The dissection of the ureter is carried on through the bladder wall on the ventral surface (or superior surface as seen in the operating position) of the ureter. The bladder is then opened in the direction of the skin incision, exposing the ureteral catheter as it disappears through the ureteral orifice. Just superior to the ureteral orifice the point at which the dissection of the ureter was extended through the bladder wall can be identified. A vein retractor is placed in this opening and the partially dissected intramural ureter is then visible in the depth of this opening. The dissection of the intramural ureter is then completed in such a manner that the entire intramural ureter is freed from the detrusor fibers except in the region of the attachment of the ureter to the trigone. This is left intact. Two or three centimeters of ureter are then pulled into the bladder and the defect in the bladder wall which was created by the dissection of the intramural ureter is closed under the newly created intravesical ureter with interrupted sutures of No. zero chromic catgut. These sutures should include bladder mucosa and muscularis. Usually three such sutures are required to repair the bladder under the ureter snugly. An anchor suture is then taken between the wall of the ureter and the bladder at the point where the ureter disappears into the bladder. Attention is then directed to the outside of the bladder at the point where the ureter disappears into the bladder. Just below this point is the defect in the bladder wall which was created by the dissection of the intramural ureter and was closed from within the bladder. To strengthen the closure of this defect 1 or 2 No. zero chromic sutures are placed through the serosa and muscularis from outside the bladder. The bladder is then closed in the usual manner using two layers of catgut sutures. Drains are left in the region of the lower ureter and in the space of Retzius. The wound is closed in layers in the usual manner and a Foley catheter is passed into the bladder per urethram and left indwelling.

The drains are removed on the second day and the ureteral catheter on the fifth or sixth day. The urethral catheter is left in for several weeks.

Case 1. A 28 year old white male paraplegic with a complete cord lesion at D10 was injured when he fell from a tree in November 1948. Repeated cystograms revealed a complete left reflux with hydro-ureter and hydronephrosis bilaterally. Emptying from the left kidney and ureter was very slow. Clinically, he had repeated attacks of chills and fever and left flank tenderness.

On May 17, 1950, a plastic operation was performed on the left ureterovesical junction. His postoperative course was uneventful. Cystograms made 3 and 6 weeks postoperatively revealed no reflux. Excretory urograms made 6 weeks postoperative revealed excellent function in 5 minutes and improved emptying in 60 minutes as compared with the 60 minute preoperative pyelogram. Clinically, the patient was improved and had no chills or fever during the 7 weeks he was observed postoperatively.

This patient returned to another Veterans Administration Hospital for a checkup examination on June 19, 1951 (13 months postoperative). He had been in good health except for one episode of pyelonephritis in March of 1951. This responded promptly to aureomycin therapy. A cystogram revealed no reflux and excretory urography was normal except for slight hydronephrosis and calyectasis on the right. I am indebted to Dr. A. D. Kapcar, urologist at the Altoona, V. A. Hospital for a summary of this checkup examination.

Case 2. A 26 year old white male paraplegic was hit by a freight train in April 1949, and the resultant injury caused a complete motor and sensory loss below D10. Repeated cystograms revealed a complete left reflux; excretory urography revealed marked hydro-ureter and hydronephrosis and delayed emptying on the left. Clinically, the patient had repeated attacks of chills and fever and left flank tenderness.

On June 23, 1950, a plastic operation was performed on the left ureterovesical junction. His postoperative course was uneventful. Cystograms made 3 and 6 weeks postoperative revealed no reflux. Postoperatively the excretory urogram was normal with excellent function in 5 minutes and almost complete emptying in 30 minutes. The previously noted hydro-ureter and hydronephrosis had disappeared. Clinically the patient was much improved and had no episodes of chills and fever postoperatively. He was given a disciplinary discharge 7 weeks after the operation.

The patient returned for a checkup examination in May 1951. He has been in good health with no episodes of chills and fever since his operation. Cystograms revealed a trabeculated bladder with a faint right reflux and no left reflux. Excretory urography revealed excellent bilateral function and emptying. It also demonstrated a hydro-ureter in the lower third of the right ureter. Cystoscopy reveals the transplanted left ureter in its new position and a saccule around the right ureteral orifice.

Case 3. A 25 year old Negro paraplegic with a complete lesion at D4 and D5 received his injury in an automobile accident in May 1950. Repeated cystograms revealed a bilateral reflux but no hydronephrosis or hydro-ureter. Clinically the patient suffered from repeated attacks of chills and fever and severe massive spasms of his legs.

On August 31, 1950, a plastic procedure was attempted on each ureterovesical junction. The operation proved technically very difficult due to severe pericystitis. The left ureterovesical junction was treated as described, but on the right an attempt was made to dissect the intramural ureter solely from within the bladder. It was believed at the conclusion of the procedure that it was unsatisfactory technically. Postoperatively the reflux has persisted. Postoperative pyelograms show excellent function bilaterally with no hydronephrosis or hydro-ureter. Clinically, the patient remains well and has no urinary tract symptoms except for chills and fever whenever his urethral catheter is removed.

Case 4. A 30 year old white male paraplegic had a complete lesion at D10 from a gunshot wound in August 1944. Repeated cystograms revealed severe bilateral reflux with bilateral hydro-ureter and hydronephrosis of a marked degree. Excretory urography revealed good function bilaterally but delayed emptying from each kidney on the 30 minute film. Clinically, the patient had no symptoms referable to the reflux except occasional pain in one or the other flank especially associated with straining to void.

On October 23, 1950, a plastic operation was performed on the left ureteropelvic junction. His postoperative course was uncomplicated. Cystograms made 3 weeks after this operation revealed no reflux on the left although reflux on the right persisted. Postoperative excretory urograms revealed excellent function in 5 minutes and almost complete emptying in 30 minutes on the left.

The patient returned for a checkup examination in June 1951. Clinically he has been well during the 8 months since his operation except for occasional right flank pain. Cystogram revealed no reflux on either side. Excretory urography reveals excellent function bilaterally. On the left there is calyectasis with no hydro-ureter or hydronephrosis. On the right there is calyectasis, hydronephrosis and hydro-ureter. Cystoscopically, the left ureter is in its transplanted position. On the right there is a definite saccule around the ureteral orifice.

Case 5. A 25 year old white male paraplegic had a complete lesion at D11 resulting from a fall in November 1949. Repeated cystograms revealed a right reflux, complete. Excretory urography revealed excellent function bilaterally with a mild hydronephrosis of the right kidney. Clinically the patient had no symptoms other than pain in right flank associated with the act of voiding.

On November 11, 1950, a plastic operation was performed on the right ureterovesical junction. His postoperative course was uneventful. Six weeks after operation a cystogram showed reflux still present on the operated side and also reflux on the left. Postoperative excretory urograms showed excellent function bilaterally and excellent emptying on the 30 minute film. Clinically the patient is in good health but he continues to have occasional pain in the right flank associated with voiding.

Case 6. A 27 year old white paraplegic had a complete lesion at D10 resulting from an accident in a coal mine in May 1947. Repeated cystograms revealed a complete left reflux. There was no hydro-ureter or hydronephrosis present. Excretory urograms were essentially normal. Clinically he complained of vague pain in the left flank especially when he strained to void.

On November 29, 1950, a plastic operation was performed on the left ureterovesical junction. Postoperatively everything went wrong. Several hours after the operation he pulled out both the ureteral and urethral catheter. No effort was made to replace the ureteral catheter. The patient did well in spite of this and a cystogram 5 weeks after the operation revealed no reflux. His postoperative pyelogram revealed excellent function in 5 minutes and almost complete emptying in 30 minutes. There was no hydronephrosis or hydro-ureter. Clinically the patient had been in excellent health since the operation. He is voiding and has no flank pain associated with this act.

Case 7. A 26 year old white male paraplegic had complete paralysis of both lower extremities as a result of a shrapnel wound in April 1945. Repeated cystograms revealed a complete right reflux. He had no hydro-ureter or hydronephrosis. Excretory urograms were normal. Clinically he had no symptoms referable to his reflux except occasional pain in the right flank.

A plastic operation was performed on the right ureterovesical junction on December 21, 1950. His postoperative course was uneventful. Checkup examination 5 weeks after the operation revealed no reflux. Excretory urography revealed excellent function in 5 minutes and excellent emptying in 30 minutes. There was no hydro-ureter or hydronephrosis.

Clinically the patient is improved and no longer has his right flank pain.

Case 8. A 26 year old white male paraplegic had an incomplete lesion at D12 as a result of a gunshot wound in August 1944. Repeated cystograms revealed complete right reflux. There was no hydronephrosis or hydro-ureter. Excretory urograms were normal. Clinically he had no symptoms referable to his reflux except occasional pain in the right flank.

On January 4, 1951, a plastic operation was performed on the right ureterovesical junction. His course was uncomplicated for the first four days and on the morning of the fifth postoperative day his ureteral catheter was removed. That night he noticed a dull ache in the right flank. The next 5 days he had an elevation of temperature (100 to 101.6F). This subsided on aureomycin. Two weeks postoperatively excretory urography revealed some calyectasis and delayed emptying of the right kidney. A checkup examination 3 weeks after operation revealed no reflux. Excretory urography revealed excellent function in 5 minutes and excellent emptying in 30 minutes and no hydronephrosis or hydroureter. Clinically the patient is well and has no more flank pain.

Case 9. A 51 year old white male paraplegic with a complete cord lesion at D12 was injured in a slate mine accident in October 1944. Repeated cystograms revealed bilateral complete reflux with a slight hydronephrosis bilaterally. Excretory urograms revealed excellent function with good emptying bilaterally. Clinically the patient had repeated episodes of chills and fever and bilateral flank pain.

On April 25, 1951, a bilateral ureterovesical plastic operation was performed. His postoperative course was uneventful. Four weeks postoperatively a cystogram revealed no reflux. Excretory urography disclosed excellent function and emptying bilaterally. He was checked again 4 months postoperatively and again cystogram revealed no reflux and excretory urograms were normal. Clinically, he is much improved and has been free of symptoms of pyelonephritis since his operation.

DISCUSSION

The first question asked of any operation designed to correct reflux is, of course, how well does it accomplish its prime purpose. In our series of 9 cases, the reflux was stopped in 7 cases (or 78 per cent). It should be mentioned that in 1 case (case 3) the operation was not technically satisfactory. With this in mind it can be said that in the 8 cases in which the criteria of the operation were met, the reflux was stopped in seven. Unless there is a careful analysis of the pre- and postoperative renal function, the mere stoppage of reflux is meaningless. In our 9 cases, three had hydronephrosis, hydro-ureter and delayed emptying preoperatively (cases 1, 2, and 4). Six had essentially normal upper urinary tracts. The 3 cases in which there was damage to the upper urinary tract showed less hydronephrosis and hydro-ureter and better emptying after the operation. Of the 6 cases which had normal upper urinary tracts preoperatively, none were damaged by the operation.

Careful analysis of our cases with special reference to the postoperative appearance of the operated ureterovesical junction shows that the success of the operation depends upon the transplanted ureter remaining in the position achieved at operation. In our seven successful cases, postoperative cystoscopic examinations show the operated ureter to lie well within the bladder and on top of the bladder mucosa. In the 2 cases which failed, the postoperative cystoscopic appearance of the ureteral orifice appeared almost the same as before the operation. For some reason, the ureter placed intravesically at operation failed to remain in its new position. (See cases 3 and 5.)

Postoperative complications occurred in cases 6 and 8. In case 6, the ureteral catheter came out a few hours postoperative. In spite of this, the postoperative results were excellent. In case 8, pain in the flank and temperature elevation occurred shortly after the ureteral catheter was removed on the fifth day. After 5 days, the last two of which the patient was on aureomycin, the pain disappeared and the temperature returned to normal. An excretory urogram 14 days postoperative showed mild calyectasis and delayed emptying in 30 minutes. A second pyelogram 1 week later demonstrated the return of normal cupping of the calyces and excellent function in 5 minutes and complete emptying in 30 minutes. This temporary obstruction was probably due to slight edema at the operative site.

Experience with the operation has taught us that the intramural ureter is more easily dissected from the bladder muscularis from outside of the bladder than from within the bladder. In our first 3 cases we dissected the ureter to the bladder and then opened the bladder and tried to dissect the intramural ureter. Difficulty encountered during this was a major factor for the failure of case 3. We have subsequently learned that when approached from outside of the bladder, the intramural ureter dissects away from the bladder muscularis quite easily. We now carry this dissection of the ureter completely through the bladder wall, especially on the ventral surface before opening the bladder.

We have no satisfactory explanation for the failure of case 5. It is conceivable that we used a ureteral catheter which was too rigid. Since the transplanted ureter is arched somewhat when properly fashioned, a stiff catheter left indwelling for several days could straighten the ureter and defeat the purpose of the operation. At any rate, we plan to use a catheter more supple than a No. 7 polyethylene catheter in the future.

SUMMARY AND CONCLUSIONS

This essay concerns itself with vesico-ureteral reflux in paraplegic patients. The high incidence of reflux in paraplegia and the severe renal damage resulting from this reflux is emphasized. Of 14 urological deaths among paraplegic patients in this hospital, nine have been due to reflux and its direct complications. Of 55 patients with reflux, 19 kidneys have required diversionary operations (17 nephrostomies and two skin ureterostomies) to preserve their dying function.

The past experimental work done on the ureterovesical junction is discussed. From this it is concluded that the anatomy of this structure is carefully planned to aid it in performing its function, i.e., that of propelling urine from the ureter into the bladder and that of preventing the reflux of bladder urine back into the ureter and kidney pelvis.

Evidence gained from the cystogram and from cystoscopy which demonstrates certain anatomical changes in the bladder at the point where it is pierced by the ureter is presented in detail with accompanying cystograms. It is concluded that reflux is due to a loss of supporting bladder muscularis behind the intravesical portion of the ureter.

Based on these conclusions, an operation designed to correct this defect is presented. The operation has three principles: first, the attachment of the ureter to the trigone is preserved; second, a long intravesical ureter is constructed and, third, the postulated defect in the bladder wall under the intravesical ureter is repaired.

The operation per se is described. It has been performed on nine patients Each of these cases is discussed in detail.

A summary of the operative results shows that the reflux was prevented in seven of 9 cases. The function and emptying of the involved kidney was improved in the 3 cases in which it was damaged preoperatively. In the 6 cases in which function and emptying were normal preoperatively, no change was noted in the postoperative studies. Although at this point we have no long time follow-ups, we have been very gratified by the initial success of this operation. We believe that we now have a form of therapy which affords an excellent change of success to offer the paraplegic patient with reflux.

The author wishes to express his deep gratitude for the encouragement, consultations and surgical assistance rendered by his sponsor, Dr. R. C. Bunts, Chief of the Urologic Service at this hospital and to Dr. A. I. Dodson, Consultant in Urology.

The author also wishes to take this opportunity to thank Miss Nerelle whose fine medical illustrations proved of great help in this undertaking.

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DISCUSSION

DR. HERBERT S. TALBOT (Framingham, Mass.): It is a particular satisfaction to have been asked to open this discussion, for this is a problem with which I have long been concerned. Several years ago, while I was at McGuire V. A. Hospital, Dr. Bunts and I were trying desperately to find a factor which might account for at least some of the cases of progressive renal destruction in paraplegics. Having gone over many pyelograms, we saw this phenomenon of reflux being repeated in a significant number of our cases of hydronephrosis, and we looked at each other with a wild surmise. Three years ago, at the Boston meeting, I had the honor of presenting our first findings.

Dr. Hutch's beautiful studies confirm the observations made since then among another group of paraplegics at Cushing V. A. Hospital in Framingham. The almost constant association with trabeculation and sacculation must surely be significant, yet the occurrence of these without demonstrable reflux in many instances suggests that other factors may be involved. Pressure alone will not produce reflux through a normal ureterovesical orifice in the adult, and any neurogenic component has, I think, been pretty well excluded as a direct etiologic agent. Infection and fibrosis imposed upon a bladder wall already trabeculated during an earlier period of decompensation might well produce an achalasia of the orifice, particularly when it is within or adjacent to a saccule. This is frankly a plea for adequate early treatment.

The occurrence of what Dr. Hutch calls the notch sign is so regular as to call for explanation. His interpretation of this finding is most ingenious, and although we cannot say today whether or not it tells the whole story, he is surely justified in using it as a basis for his reasoning. Because, whatever its exact explanation, this notch, or the ureteral gap, as we call it in our clinic, is almost certainly an evidence of obstruction, presumably functional in character, and it is this obstruction, rather than mere backflow, which leads to disaster.

Regarding treatment, I am fascinated by the ingenuity of the operation described this morning, and shall await with great interest the results of a longer follow-up. To us at Cushing, as to our colleagues at McGuire, it has become apparent that ureterovesical re-implantation is not the answer. My chief fear is that any plastic operation, however soundly conceived and executed, is vulnerable to the danger that the same etiologic factors continuing to act may bring about a recurrence. As Dr. Hutch has very properly pointed out, the etiologic association of reflux with certain pathological changes does not necessarily mean that correction of the reflux itself will adequately correct those changes. But it has apparently been his experience, as it has been mine, that so many of these patients go on to ultimate renal insufficiency that a prophylactic procedure, properly timed, has a real place in treatment and he has therefore operated upon some patients whose upper urinary tracts were still essentially normal.

Because, in recent years, a few patients seem to have avoided serious consequences if carefully managed, it has not been my policy to operate until hydronephrosis is apparent, but before there is recognizable functional impairment. Admittedly, this is a type of temporizing which would not be justifiable if a definitive and dependable prophylactic procedure were available. Dr. Hutch's operation may be just that. This is not the occasion for describing my own operative approach, save to say that it isn't as good as this one if this one works. Whether it does, or whether, as is so often the case, it will have to be variously modified in technique or application, there is no doubt in my mind that Dr. Hutch has made a valuable contribution in a field where it was much needed, and I for one am grateful.

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LEIOMYOSARCOMA IN DIVERTICULUM OF THE BLADDER

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Cancer arising in a diverticulum of the urinary bladder is not a rare finding, having been recorded almost one hundred times in the literature. Muellner[1] pointed out that many cases are not reported, and the incidence is probably higher than the figures usually given (1.6 to 2.3 per cent).[2] Leiomyosarcoma of the urinary bladder has been reported only 24 times. Kretschmer and Doerking[3] reviewed fourteen cases in 1939. Crane and Tremblay[4] added seven more in 1943. Lev and Bell[5] reviewed the previous cases and added a case of their own. Mackles et al.[6] presented a case in which leiomyosarcoma occurred simultaneously with carcinoma, while Petkovic[7] reported a case with spontaneous rupture of the tumor. We have been unable to find any report of leiomyosarcoma occurring in a bladder diverticulum, which makes the following case unique.

CASE REPORT

No. 138623, L. D., a 67 year old white man, entered the hospital on February 17, 1950, complaining of hematuria of 1 week's duration which began as a slight intermittent discoloration of the urine and grew progressively worse until the day of admission, when he passed large clots with marked dysuria. His past history was noncontributory except that he had lost about 20 pounds in the past 6 months.

The patient was a thin, asthenic white man. The oral temperature was 102F. The findings on physical examination were not remarkable except for a moderate elevation in blood pressure, 170/100, and slight tenderness to palpation in the suprapubic area.

Laboratory data: erythrocytes 4,310,000; leukocytes 13,000, and hemoglobin 12.8 gm. Urine: reddish brown in color; specific gravity 1.024; pH 5.5; albumin, trace; sugar; negative; microscopic, 10 to 12 white cells and 40 to 50 red cells per high power field, with a moderate number of bacteria. The nonprotein nitrogen was 30 mg. per cent.

On penicillin and gantrisin therapy the temperature promptly receded to normal, the dysuria disappeared, and the hematuria decreased. Excretory urography revealed a normal upper tract, and an oblong shadow on the right side of the bladder interpreted as a diverticulum. At cystoscopy under pentothal anesthesia a 24F Brown-Buerger cystoscope was easily introduced. The ureteral orifices were normal as were the vesical neck and posterior urethra. On the right posterior wall, just medial to the right ureteral orifice, was a diverticular opening about 1 cm. in diameter. This corresponded to the location of the diverticulum seen on the excretory cystogram. On the left lateral wall, about 3 cm. from the air bubble, a papillary tumor was seen. The surface was necrotic. The base was estimated to be about 2 by 2 cm., and it could be seen that the tumor was protruding from the neck of another diverticulum. The necrotic surface of the tumor did not appear favorable for biopsy. While the patient was under anesthesia two fingers were inserted into the rectum, and a mass about the size of a golf ball could be felt by bimanual palpation. X-rays of the chest, spine, and pelvis revealed no metastases. It was decided to perform a resection of the tumor and the diverticulum, with a preoperative diagnosis of papillary carcinoma in a bladder diverticulum.

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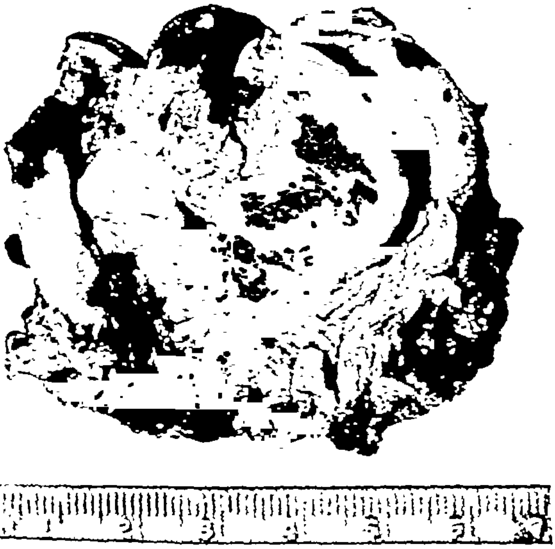

FIG. 1. Surgical specimen. Peripheral cuff of baldder mucosa is seen, with central mass of necrotic tumor projecting from diverticulum. Diverticulum opening is seen as a crescential slit around upper right border of mass.

The procedure was done under spinal anesthesia. The diverticulum containing the tumor arose on the left lateral wall and extended downward and laterally. With some difficulty, it was freed from the distal end of the left ureter. The bladder was opened in the midline and a racquet incision extended from that point excising the diverticulum and a cuff of bladder wall about 2 cm. wide. The other diverticulum on the right side was inverted and excised. Fifty per cent alcohol was applied to the bladder mucosa and surrounding tissue where malignant cells might have dropped. The bladder was closed around a suprapubic drainage tube. This was removed in five days, and replaced by an indwelling urethral catheter. The report on the surgical specimen follows.

The gross specimen (fig. 1) consisted of a 5 cm. spherical mass of bladder wall which in its central portion showed an opening lined by light grey mucosa. The major part of the opening was filled with a large tumor nodule which projected from the mouth of the diverticulum, and was hemorrhagic and mottled light and dark red. Strands of grey-white tissue could be seen coursing through this large mass. The surrounding bladder wall was somewhat hemorrhagic, but not remarkable otherwise.

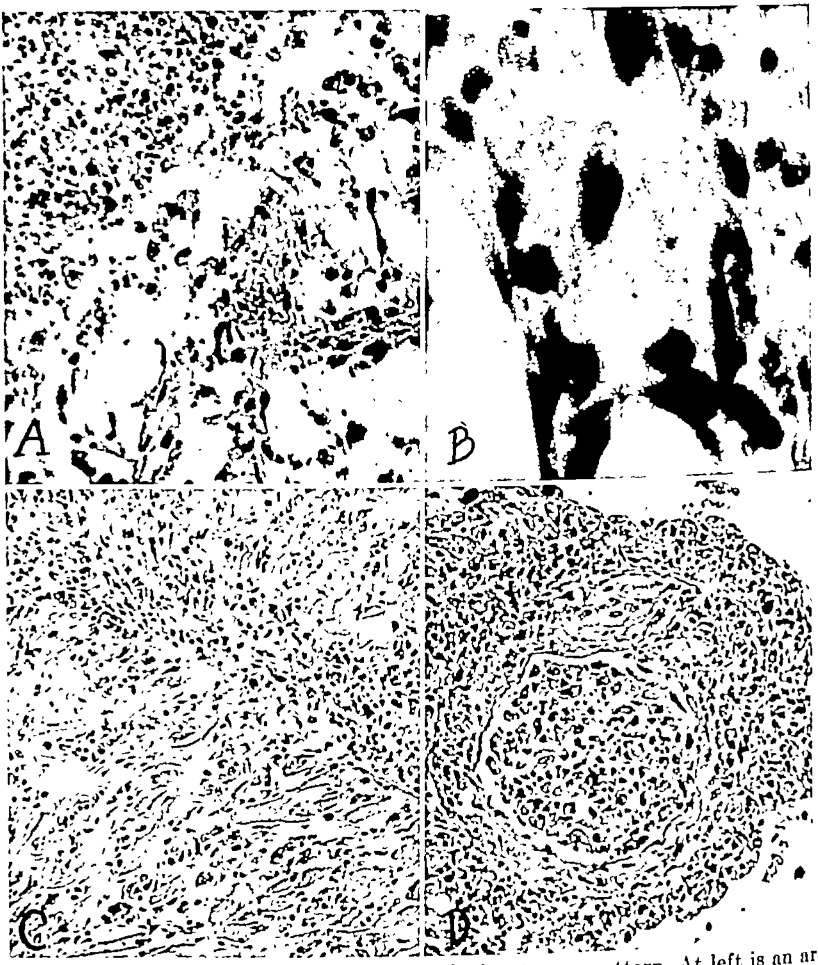

FIG. 2. *A*, low-power view showing the interlacing tumor pattern. At left is an area of necrosis. H & E stain. *B*, high-power showing irregular fusiform tumor cells, which take "red" portion of trichrome stain. Trichrome stain. *C*, showing tumor invading heart muscle. H & E stain. *D*, showing tumor embolus in blood vessel of lung. H & E stain.

Microscopic sections (fig. 2, *A* and *B*) showed marked superficial necrosis with acute inflammatory reaction in all portions. The main tumor mass was composed of interlacing strands and bundles of spindle cells which exhibited marked variations in size and shape, but usually possessed a vesicular nucleus with a fairly prominent nucleolus. The stroma was quite vascular, and there were focal hemorrhages throughout. A section of the bladder from the margin of the specimen did not show any tumor, but did show marked chronic inflammation with squamous metaplasia. In one or two places in the tumor there was seen invasion of tumor cells into blood vessels.

The patient was discharged on the twentieth postoperative day, having been ambulatory since the second postoperative day. The suprapubic sinus failed to close and tumor tissue began to protrude from it. In spite of a course of deep x-ray therapy, the patient had a rapid downhill course and expired 2 months postoperatively. An autopsy was performed with the following findings:

The body was well developed but quite emaciated. The previously described suprapubic incision was noted, and there was a sinus tract at its upper end. There was massive tumor involvement in the entire pelvis. In addition, tumor metastases were noted in several locations. A somewhat unusual location was the right ventricular surface of the heart, which contained several small grey-white nodules in the epicardium, and penetrating the entire thickness of the right myocardium (fig. 2, *C*). The lungs contained innumerable tiny raised grey nodules, which occasionally were confluent. In the right middle lobe there was a 5 cm. nodule of tumor which showed central softening (fig. 2, *D*). In the abdominal cavity, the peritoneum generally was free of tumor but the pelvic peritoneum showed numerous metastatic nodules as well as marked thickening. The stomach contained an 8 mm. metastatic nodule on the lesser curvature near the cardia. There were several metastatic nodules in the liver and spleen. The left kidney showed pyohydronephrosis and acute pyelonephritis, and was larger than the right. The right kidney was essentially normal. Other gross findings included a large esophageal diverticulum, and multiple para-aortic nodes containing yellow-grey metastatic tissue.

Microscopic examination revealed the tumor to be metastatic to the adrenals, which had not been noted grossly. The gastric nodule proved to be largely inflammatory in nature, but contained a large lymphatic plugged with tumor cells. Due to marked tumor overgrowth the gross autopsy did not well delineate the bladder. It was adherent to all the contiguous structures, and the mucosa was almost completely replaced by the soft grey nodules of tumor. Microscopically there was seen tumor tissue involving all coats of the bladder, and extending to all contiguous structures, including the prostate, which had most of its posterior lobe replaced by tumor. Special stains on the tumor included a connective tissue stain (trichrome), which showed the tumor cells to take the stain for smooth muscle, as well as a silver stain.

Other interesting features of the tumor included the presence of tumor emboli in multiple vessels throughout, particularly in the epicardial and pulmonary vessels. The occurrence of leiomyosarcoma in the spleen was presumed not due to direct involvement, but rather secondary seeding from the heavily involved lungs.

DISCUSSION

All but one of these reported cases of leiomyosarcoma of the bladder have been rapidly fatal. In retrospect one wonders if a preliminary biopsy would have revealed the nature of the tumor and if radical surgery would have influenced the outcome. Because muscle fibers are so sparse in bladder diverticula, we assumed that only epithelial tumors arose in them. Since the presenting portion of this tumor was necrotic, the base inaccessible, and the tumor bleeding, it was thought that no useful information would be gained by biopsy. However, our experiences in this case would indicate that a biopsy, even from an unfavorable site, might establish the type of tumor even though it gave no indication of the extent of penetration.

In view of the rarity of occurrence of malignant muscle tumors within diverticula of the bladder, the surgical and autopsy material was furnished the Armed Forces Institute of Pathology and the registry of urologic pathology for review. It was the concensus of the staff at that institution that the lesion was "a myosarcoma of the diverticulum of the urinary bladder with metastases." They continued "in some of the H & E sections one almost imagines the existence of cross striations but they have not been convincingly demonstrated." We, through special stains, had attempted also to elucidate the question of striations in consideration of a possible rhabdomyosarcoma but were unable to establish this fact. The staff at the registry of urologic pathology also agrees that this case is quite unusual.

SUMMARY

A case of leiomyosarcoma in a diverticulum of the urinary bladder is presented, being the only such case, to our knowledge, reported in the literature.

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PODOPHYLLIN IN TREATMENT OF HUMAN ADENOCARCINOMA OF BLADDER

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Podophyllin is a resin derived from the roots of the mandrake plant and has been in use for at least a century as a laxative. Considerable interest was aroused when it was demonstrated that a suspension of the resin in oil was highly effective against condyloma acuminata.[1] Successful topical application in the treatment of human papilloma of the bladder has been reported.[2, 3] The effect of the resin on transplanted mouse tumors has been investigated.[4, 5] Its selective damaging effect on mouse tumor cells as compared with normal cells has been shown.[6] Observations have been made on its slight anticarcinogenic action.[7]

There recently came under our observation a case of adenocarcinoma in exstrophy of the bladder. The patient was a white man of 53, who presented a typical exstrophy of the bladder with epispadias. During the past year he had noted a "growth on the bladder." The right ureteral orifice could be identified and urine was seen issuing from it. The left orifice could not be seen and no urinary drainage was noted from this side. The left half of the bladder epithelium was elevated and covered with a rather uniform, reddish type of growth. Excretory urography showed a right hydronephrosis and hydro-ureter and nonfunction of the left kidney.

It was decided to test the effect of podophyllin on the tumor and the following materials were used: Podophyllin, n.f., 10 per cent suspension in mineral oil was applied to the entire exposed bladder daily in amounts of 10 cc. The oily suspension was held in place by three layers of surgical gauze. Biopsies taken of the bladder epithelium showed transitional cell carcinoma, but subsequent sections made after the bladder and metastatic lymph glands were removed surgically, proved the neoplasm to be adenocarcinoma. Biopsies of the tumor were taken at 8 and 21 days of therapy.

There was no necrotizing effect on the tumor as observed in venereal warts. No areas appeared to change in color or consistency and the noncancerous portion of the bladder epithelium remained unchanged. There were no central nervous system effects, although at the end of a week, he did complain of one period of vertigo and slight abdominal cramps. This entirely disappeared and did not reappear during the course of the therapy. The tumor continued to grow and two and a half months later had spread over the bladder epithelium until it encroached upon the right ureteral orifice. Biopsies at the end of eight

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Aided in part by a grant from the Iowa Division of the American Cancer Society.

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and twenty-one days showed the tumor cells to be healthy, and no structural alterations were noted. The tumor reduced triphenyl tetrazolium chloride before and after therapy.

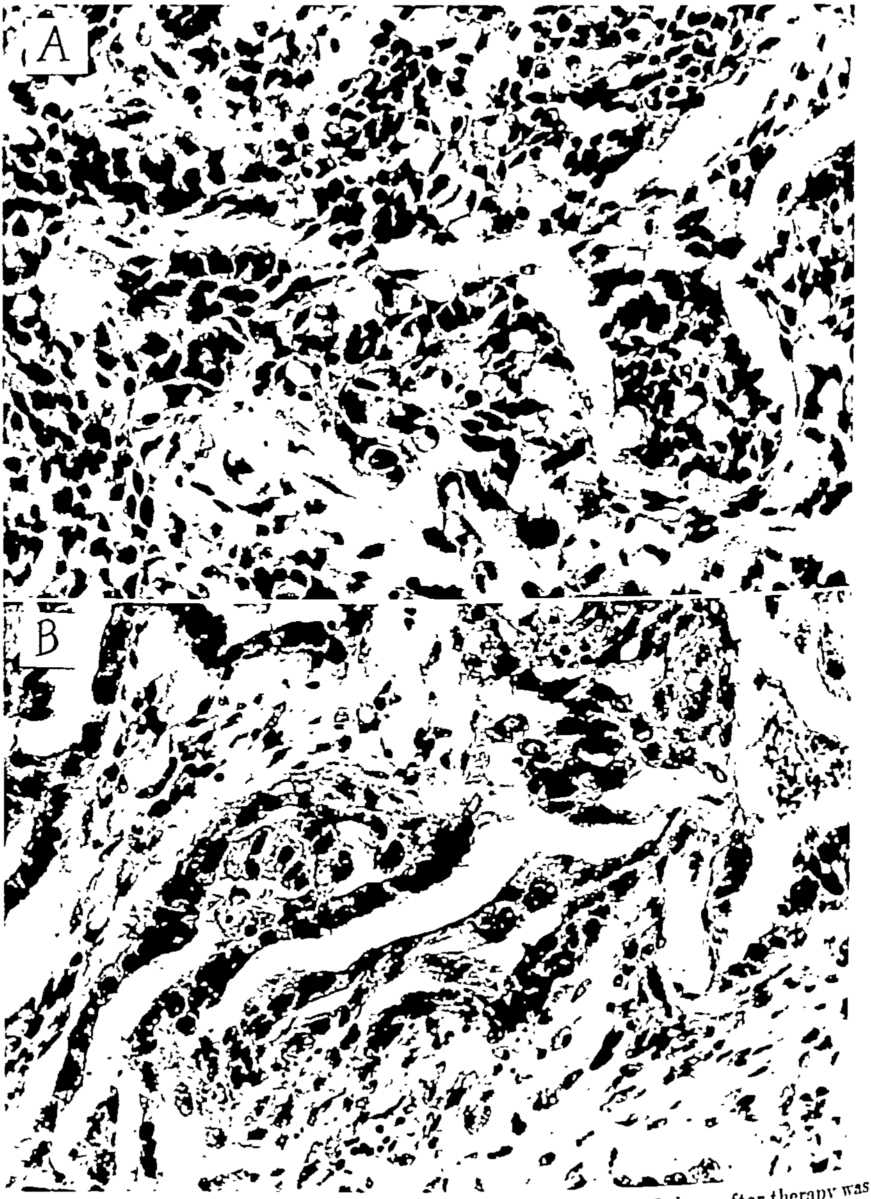

Fig. 1. *A*, biopsy specimen before therapy. *B*, biopsy specimen 8 days after therapy was started. H & E stain.

CONCLUSIONS

A 10 per cent suspension of podophyllin in mineral oil, applied directly to a human adenocarcinoma of the bladder in amounts of 10 cc daily for 3 weeks had no demonstrable adverse effect upon the growth of the neoplasm.

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TREATMENT OF EPISPADIAS: A REPORT OF 18 CASES

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Epispadias, fortunately one of the rarest of congenital anomalies, is one which can be most tragic. It occurs both in the male and the female. Dees, in 1949, reported its incidence from a study of the files of eight large hospitals in this country and found a proportion of 1:117,604 in males and 1:481,110 in females. Our series shows a similar ratio of 5 to 1 in males and females. Many methods for the correction of this malformation have appeared in the surgical literature during the last 75 years. When many different methods of repair are advocated it is safe to assume that there have been many failures. This paper is a report of the operative results in 18 cases of epispadias treated at the Children's Hospital of Boston during the past 20 years. It is intended to emphasize that the malformation can now be suitably corrected in most instances.

EMBRYOLOGY AND PATHOGENESIS

Epispadias may be of varying degree. A clear understanding of the development of the urogenital organs is helpful in the successful surgical repair of this anomaly. In 1900, Hart summarized the important features in the development of the urogenital system from his review of the observations of Kolliker, Graf Spee, Lieberkuhn, Tourneux, Keible, and others. Since then Von Geldern, Arey, and Bremer have reported their work on the anomalies of epispadias and exstrophy of the bladder.

In the early formation of the flat 1.5 millimeter human embryo, behind the primitive knot there develops on the dorsal surface the primitive groove and behind this the cloacal membrane. Bremer feels that these two areas, the primitive groove and the cloacal membrane, should be called the primitive plate. This primitive plate is behind the primitive knot in the stage of the flat embryo, but the plate becomes ventrally placed as the embryo grows. At this stage the embryo begins to assume the characteristic curved form as the caudal and cephalic ends flex toward each other. By this bending during its growth, the caudal end of the primitive plate migrates toward the base of the umbilical cord, whereas the cephalad end of the plate lies toward the base of the tail bud.

The primitive plate is made up of entoderm and ectoderm only. However, just to either side of it there is mesoderm between entoderm and ectoderm. The caudal end of the cloaca is covered in the midline by the primitive plate. The cloaca in the 5.0 mm. (5 weeks) embryo is a common vestibule for the hindgut, the allantois, and the mesonephric ducts. This cloaca is of considerable depth (ventrally and dorsally) but is compressed from both sides by mesenchyme. As the embryo grows, the mesenchyme grows in and fuses in the midline from above downward, thereby dividing the cloaca into two tubular structures, the rectum dorsally and the urogenital sinus ventrally. This separation into two parts takes place at the 9-11 mm. stage.

In the formation of the perineum a small portion of the primitive plate is left covering the hindgut and here is subsequently formed the caudal opening of the rectum, the proctodeum. The remaining cephalad portion of the primitive plate covers the urogenital sinus and the ventral abdominal wall of the embryo. It is during this stage of development that mesodermal segments or masses grow in from the sides toward the midline. These mesodermal projections meet first above and progressively join downward between the layers of the primitive plate, thus forming the ventral abdominal wall and the genital tubercle. The ventral surface of the genital tubercle retains a portion of the primitive plate. As the genital tubercle grows, the remaining portion of the primitive plate becomes the primitive urethra and grows with it. With this growth the genital tubercle forms the phallus and the lateral constituent parts of the genital tubercle meet in the ventral midline to form the median raphe. In this way, there is formed a tubular structure (the urethra of the male) from the primitive plate.

Malformations of the bladder and urethra are the result of an arrest or an abnormality of development, occurring in the fifth to eighth week of embryonic life. These anomalies occur when there has been a failure of union in the midline of the lateral mesodermal masses. The failure to join may be total or in part, which explains the varying degrees of malformation.

Exstrophy of the bladder is a total failure of the mesodermal masses to join in the midline from above downward, leaving the primitive plate which consists of only ectoderm and entoderm. This very thin structure may yield or cleave during the growth of the embryo and so expose the bladder or any part of it depending on the degree of union of the mesoderm in the midline. The epispadias so produced would be complete and epispadias or any degree thereof may be explained on the failure of the genital tubercle to be formed properly. In cases of epispadias the primitive plate remains on the dorsum of the genital tubercle, and as the genital tubercles join ventrally, a dorsal defect is produced by the nonunion of the mesodermal masses. So it will be seen that as the phallus is developing the primitive urethra grows with the genital tubercle, but if there is failure to join normally it does not form a tubular structure but produces a flat penis and glans. Such a penis is small and is usually curved upward against the abdominal wall. Any degree of epispadias can occur, producing penopubic, penile, or balanitic forms of the condition.

Hypospadias, on the other hand, is produced by the failure of the genital tubercle masses to meet in the midline ventrally at any place along the median raphe from the base of the shaft to the glans.

CLINICAL PICTURE

In the male there are three forms of epispadias:

1) *The balanitic type* is the most uncommon. The defect extends dorsally from the coronal ridge to the tip of the glans, leaving an open groove and a flattened glans. This dorsal cleft of the urethra does not extend back to the shaft, so there is no associated incontinence.

2) The *penile type* usually has a urinary meatus in front of the symphysis.

The penis is short, flat, and curved upward. The dorsal groove extends along the glans and the entire shaft; there is an extensive gutter between the corpora. Incontinence may or may not be present, depending on the degree of deficiency at the bladder neck sphincters and compressor urethrae muscles. In some cases there is separation of the pubic rami and lower portions of the rectus muscles which can permit herniation or prolapse of some bladder membrane out through the retrodisplaced urethral meatus.

3) In the *penopubic type,* the complete epispadias is usually associated with some degree of exstrophy of the bladder. In some cases it is impossible to say whether one is dealing with a complete epispadias or with a sub-symphysial exstroversion; the two conditions overlap one another. Because of deficiencies at the bladder neck, the penopubic type is always accompanied by incontinence.

The physical findings and symptoms will vary according to the type of anomaly present. When a male child has balanitic or penile epispadias, he usually has control of urination and it is only the deranged external anatomy that brings the child to the physician's attention. Sometimes the foreskin has to be pushed back before the real extent of the defect can be determined. In balanitic epispadias there is little more than a dorsal cleft of distal urethra, leaving a glans which is open and flattened. In penile epispadias the urinary meatus is situated toward the base of the penis; the penis lies open through all or most of its extent, is short, flat, and curved upward. It is important to examine the child to determine if it is possible to start and stop the urinary stream at will. If there is complete incontinence, surgical attack on the bladder neck will be necessary to cure it, but if there is only a mild deficiency of control it is often possible by sphincter muscle training exercises to improve the situation to a remarkable degree. In the male with a complete, penopubic epispadias there is a dorsal groove-like slit along the entire length of the penis and an abdominal wall defect of variable extent at the base of the penis. The prepuce is pendulous and hangs entirely from the ventral surface. The flatness of the shaft of the penis comes from wide separation of the corpora cavernosa and from absence of the corpus spongiosum. The urinary opening on the lower abdominal wall often is large enough to admit the tip of an examining finger, which will go directly into the bladder; some portion of the bladder wall may actually prolapse through this orifice. The ends of the pubic bones may be separated. Incontinence is always present; the bladder is apt to be small and contracted.

In the female there are also three general types. In each of them a normal fatty mons is absent and its substance is divided into two lateral halves; the clitoris likewise is bifid. In the first type the urethral orifice appears to be quite patulous. In the second, the urethra is dorsally slit along most of its extent, but the bladder sphincters are intact and there is no incontinence. In the third type, the cleft involves the entire urethra and also the sphincters; obviously there is incontinence. In this latter form there may be some prolapse of bladder wall through the urethral opening from time to time.

In incontinent children, both male and female, urine may be retained for several hours while in the recumbent position but when erect there is more or

TABLE 1. *Summary of data from 18 cases of epispadias*

INITIALS AND SEX	AGE AT OPERATION	TYPE OF EPISPADIAS	PREOPERATIVE CONTINENCE	OPERATION DATE AND TYPE	POSTOPERATIVE RESULT
J. G., male, 297522	8	Incomplete penile (fig. 1)	Excellent	Plastic to penis, 1945	Voids well
D. G., male, 117463	3	Complete	Incontinent	Ureteral transplantation, 1930	Died, peritonitis
J. T., male, 202267	6	Complete	Incontinent	Urethroplasty, 1940. Secondary bladder neck operation, 1944	Voids with good stream. Is continent
C. F., female, 277883	2	Complete (fig. 2)	Incontinent	Plastic to urethra and sphincter, 1945	Only very slight soiling
P. S., male, 277730	4	Complete	Incontinent	Urethroplasty and plastic to sphincter, 1947	Voids with good stream. Continent
D. de F., female, 278903	7	Complete	Incontinent	Plastic to urethra and sphincter, 1944	Voids well. Continent
D. McI., male, 245356	10 mos.	Incomplete penile	Excellent	Urethroplasty, 1944	Voids well
R. B., male, 284499	4	Complete	Incontinent	Plastic to urethra and sphincter, 1946. Secondary to bladder neck, 1948	Voids well. Satisfactory continence
B. E., female, 277774	4	Complete	Incontinent	Plastic to urethra & sphincter, 1943. Secondary to bladder neck, 1946. Ureteral transplants, 1946	Good anal control after ureteral transplants

TABLE 1—*Continued*

R. A., male, 282758	5	Complete	Mild incontinence	Plastic to urethra and sphincter, 1941; Thiersch graft to urethral meatus, 1944.	Good stream and control
J. M., male, 213785	3	Complete (fig. 3)	Incontinent	Plastic to urethra and sphincter, 1948	Voids well. Continent
R. S., male, 213785	5	Complete	Some incontinence	Plastic to urethra & sphincter, 1942; Thiersch graft to urethral meatus, 1942	Excellent stream and control
W. D., male, 267234	4	Balanitic	Occasional dribbling	Plastic to urethra, 1942	Voids good stream. Continient
D. R., male, 291534	4	Incomplete penile	Excellent	Plastic to urethra, 1945	Voids with good stream
J. G., male, 347852	12	Balanitic	Incontinent in day. Dry at night	Plastic to urethra & sphincter, 1949	Good stream. Continent
C. P., male, 233699	11	Incomplete penile	Incontinent	Plastic to urethra & sphincter, 1939. Further plastic to penis, 1940	Good stream and continence
S. S., male, 299753	2	Balanitic	Excellent	Plastic repair, 1945	Good urinary stream
D. E., male, 215098	3	Complete	Incontinent	Ureteral transplants, 1940. Plastic to penis, 1943	Good rectal sphincter control. Dry

less constant wetting. As a result the regional skin becomes macerated, inflamed, and at times ulcerated.

Coitus for the male is not disturbed by minor degrees of epispadias, but with the more extensive deformities insemination is impossible because semen is discharged at the penopubic angle. In females the reproductive organs are not involved; they can reproduce normally.

TREATMENT

Indications for operative repair.—The objectives of operative repair include: 1) the relief of urinary incontinence when it exists; 2) in the male, to change the point of exit of urine and semen to a normal site, and to provide as good a cosmetic restoration of the penis as possible; 3) in the female, to carry out whatever urethral repair is necessary and to restore the vulva to a normal form.

Optimum age for operative repair.—Epispadias repairs are elective procedures, and may be done at any time in childhood; however the size of the parts impose certain limitations and give optimum ages for performing operations. Almost never should any of these repairs be done before 2 or 3 years; prior to this time the parts are apt to be so tiny that the surgeon does not have a reasonable chance at making the nicest reconstruction. We generally prefer the ages between 3 and 5 years, depending upon the size of the subject. If there is any incontinence, operative relief should certainly be offered before the child enters school.

Historical notes.—Many methods for the correction of epispadias, both complete and incomplete, with and without incontinence, have been published in the medical literature. We shall, therefore, refer to a few of the papers that have led to the methods that are generally used and which are producing the most satisfactory results. In 1845, Dieffenbach cured an incomplete epispadias of penile type by freshening up the edges of the open urethra and uniting them by direct suture. Thiersch, in 1869, found that he could successfully cover the penile type of epispadias with neighboring skin flaps. He succeeded in constructing in front of the bladder an enclosed narrow space which, by aid from a special mechanical appliance, exerted pressure at the bladder neck and overcame incontinence. In 1895, Cantwell published a classical description of his operative repair for incomplete epispadias, by infolding the urethra and bringing skin together on the dorsum of the penis. This was without question a tremendous advance in surgical therapy; unfortunately, the repair often broke down and urethral fistulas or strictures developed. In 1906, Trendelenburg thought that incontinence of complete epispadias could be cured by narrowing the muscular ring around the neck of the bladder; he was one of the first to suggest this feature. He recommended postoperative suprapubic drainage and also a stabilization of the pubic bones, feeling that this latter step might reduce lateral tensions on the repaired urethra. In 1907, Nové-Josserand and Cotte, by combining lengthening with torsion of the urethra, reported cures of the incontinence in complete epispadias. In 1911, Stiles thought that there should be better methods for ureterosigmoidostomy to care for those unfortunate children who had had previous unsuccessful plastic procedures, but he concluded that under certain conditions the ureters might be transplanted successfully to the bowel. In 1918, a new method of repair for penile epispadias (with partial or no incontinence) was published by Young. He believed that it was the lack of blood supply which caused many failures in healing of a newly constructed urethra as done by the Cantwell technique; he recommended leaving one side of the newly constructed urethra attached to the adjacent corpora cavernosa. With this method, he reported no sloughing of the urethra that had previously made Cantwell's procedure meet with so many disappointments. In 1922, Young reported his double, sphincter operation for repair of epispadias with incontinence; in 1940 he published results in 13 such cases treated by this method, with alleviation of incontinence in one and complete cure in 12.

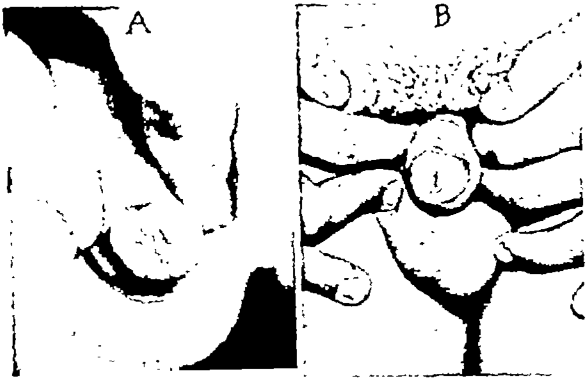

FIG. 1. *A*, incomplete penile epispadias in an 8 year old boy who had normal urinary control with a spraying urinary stream. *B*, same patient 5 years after plastic repair. Patient now has a normal appearing penis and good stream.

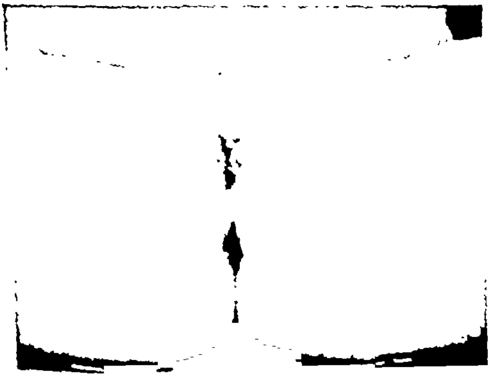

FIG. 2. Complete epispadias in a 2 year old girl. Note bifid clitoris and cleft condition of vulva. Patient was incontinent of urine.

Methods adopted in the present series.—Our general policy has been to attempt the type of repair suggested by Cantwell, of freeing the urethra, making a tube out of it and bringing together the superficial structures of the penis over this. We have not adopted the suggestion of Young of leaving one side of the urethra attached to its bed; indeed we have stressed the point of widely freeing the urethra, so that it can be displaced ventrally and permit apposition of corpora over it. The details of operative technique are probably best conveyed by the accompanying drawings. The skin sutures are removed under anesthesia on the seventh or eighth day. The suprapubic tube is withdrawn on the tenth postoperative day.

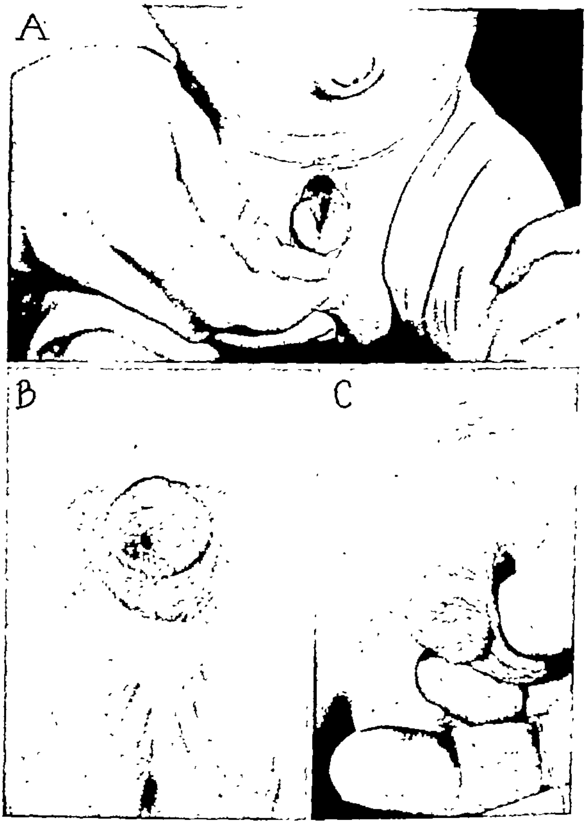

Fig. 3. Complete penopubic epispadias. Patient was incontinent. *A*, patient 6 weeks of age. *B*, *C*, same patient at 5 years, 2 years after plastic repair. He voids with good stream and has normal control.

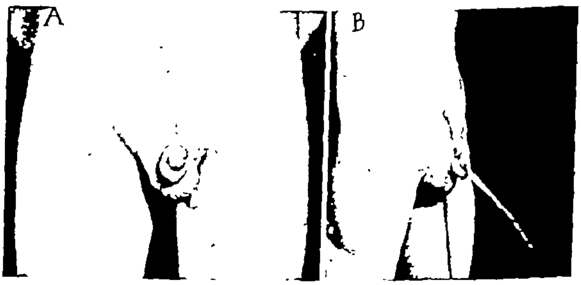

Fig. 4. Child who had complete penopubic epispadias and urinary incontinence. Postoperative photographs showing patient voiding with excellent urinary stream.

Results of therapy.—During the past 20 years, 18 cases of epispadias have been treated surgically at this hospital (table 1). There have been 3 cases of balanitic epispadias, 4 cases of penile epispadias, and 11 cases of penopubic or complete epispadias (fig. 4). All were males except three: these females all had complete epispadias.

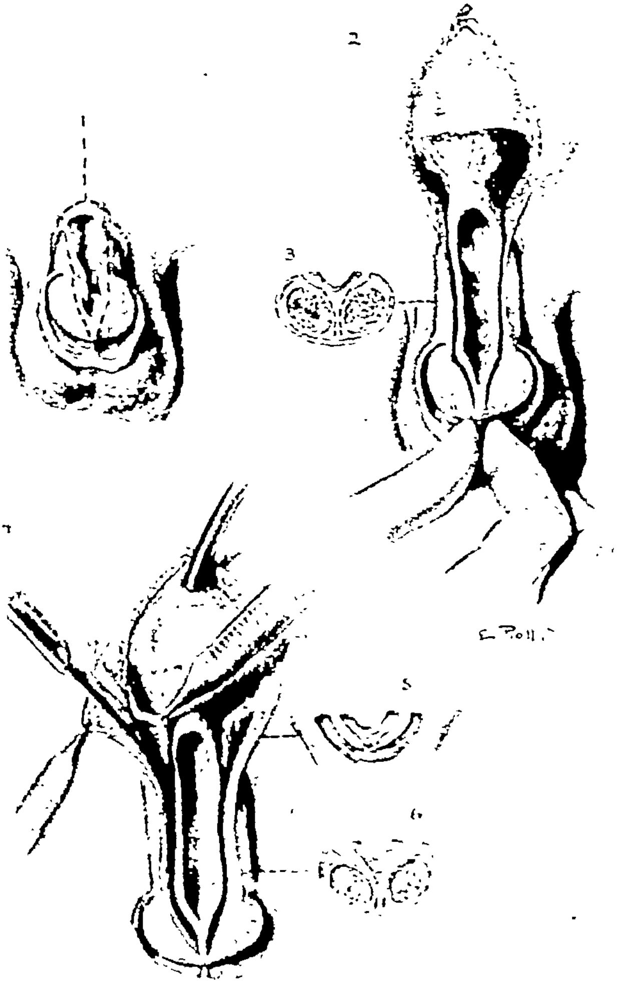

FIG. 5. Operative repair of complete epispadias. *1*, Outline of incisions. *2*, Urethra freed from its bed. *3*, Cross section sketch of penis at level indicated. *4*, Suprapubic catheter in bladder. Remnants of external bladder sphincter being freed up. *5*, Sketch showing position of sphincter *around* posterior urethra. *6*, Sketch showing deepening of dissection *between* corpora.

The 3 patients with balanitic epispadias had plastic repairs to the glans only, with good results. The 4 children with penile epispadias had urethroplasty performed, two of these had been incontinent before but are dry postoperatively. The 11 children with complete epispadias were treated in two ways. In the early part of this work, two were treated by ureterosigmoidostomy without any previous attempt to repair the bladder neck sphincters. One died (in 1930) of peritonitis. The other (operated upon in 1940) has good anal control during the 11 years he has been followed. We now believe very strongly that ureteral transplantation should never be used as a primary operation for incontinence of epispadias; it should only be used as a last resort to control incontinence if plastic attempts to repair a bladder outlet have failed. This is particularly true in the male child who is thereby made to sit down during acts of voiding. The remaining 9 children with complete epispadias have been treated by the general methods shown in figures 5, 6 and 7 (in two males the urethral meatus was made too small, and subsequently had to be enlarged by inserting a small Thiersch

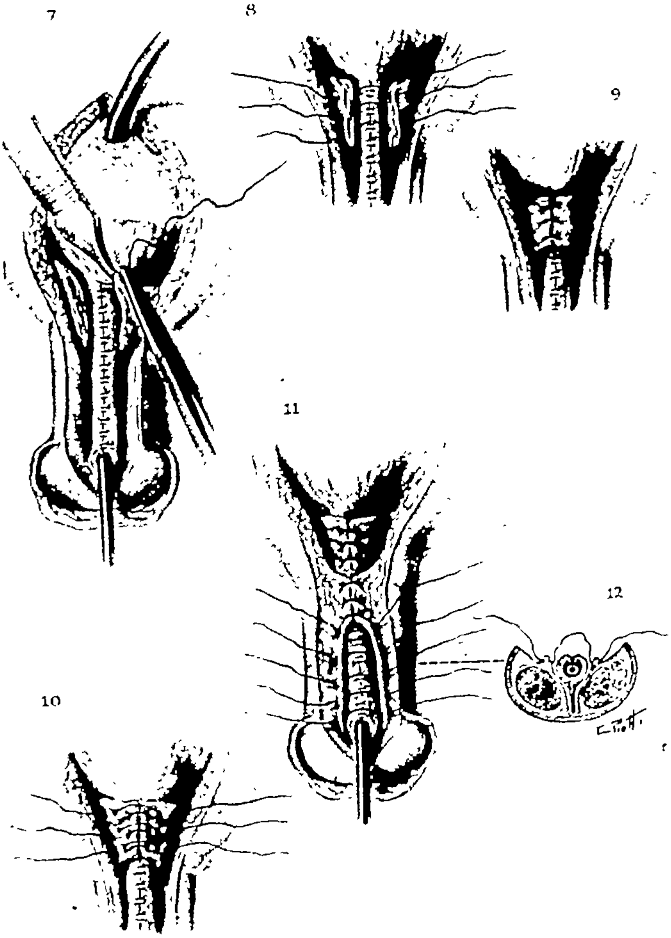

FIG. 6. Operative repair of complete epispadias (continued). *7,* Urethral tube turned inward with fine chromic catgut sutures. Repair over a No. 8 tube. Sphincter muscles being brought around urethra with silk sutures. *8,* Sutures placed for sphincter repair. *9,* Sphincter completed. *10,* Additional plication of sphincter, if necessary to make it tight. *11,* Corpora being brought together *over* urethra with silk sutures. *12,* Sketch showing placement of corpus stitches.

graft). Following operation three children had little improvement in incontinence and were re-operated upon; a further tuck was taken in the bladder-neck sphincters. Two of these then developed good urinary control, but the third required a transplantation of the ureters to the sigmoid, good anal control resulting.

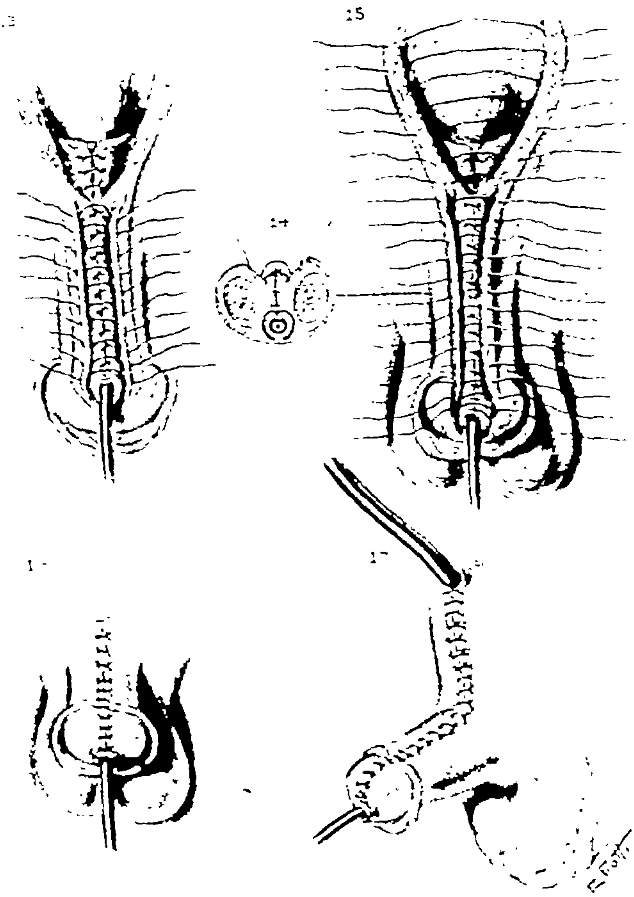

FIG. 7. Operative repairs of complete epispadias (continued). *13*, Second layer of fine silk sutures to bring corpora and sides of glans together. *14*, Sketch of approximation of corpora in a manner to displace urethra to undersurface of penis. *15*, Fine silk (00000 Deknatel) sutures in subcutaneous tissues. *16*, Skin and glans approximated. Urethral meatus sewed to glans. *17*, Final result. If desired, urethral tube can be withdrawn at this point. Suprapubic catheter must remain and be left open for 10 days.

SUMMARY

Epispadias is a rare malformation; it is about five times more common in males than females. Varying degrees of the anomaly can be encountered. The surgical problems are concerned not only with accomplishment of good cosmetic reconstruction but also with the cure of incontinence in a very high proportion of the cases.

A series of 18 cases of epispadias is reviewed. Two of the patients had ureterosigmoidostomies performed without any previous surgery performed on the bladder neck or urethra, while one had ureterosigmoidostomy after two operative attempts had failed to control incontinence. We feel strongly that ureterosigmoidostomy should be used only as a last resort for control of urinary incontinence, especially in the male subject. Every child with epispadias should have the benefits of a plastic repair to the epispadias and also to the bladder neck whenever incontinence exists. In the female, the external genitalia should be restored to a reasonable appearance. In the male, every effort should be made to provide a normal appearing anatomic structure through which urine and semen may travel; it is possible to do this successfully in the vast majority of cases.

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URETHRAL RUPTURE: EARLY AND LATE POSTERIOR COMPLICATIONS

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Crushing injuries of the pelvis and resulting laceration of the urethra and bladder are not uncommon. The most common urethral injury is a laceration which almost always takes place at the apex of the prostate.

Trauma to the urethra, other than by instrumentation, is frequently treated by the general practitioner. In most cases he sees the patients first, in the hospitals of smaller communities where the accidents occur. He may carry them along without consultation until the problems become complicated.

There are three situations that may result:

The first is the case where rupture of the urethra is operated upon immediately and a generous catheter is passed. The urethra is allowed to heal around it and no stricture is likely to form.

The second is the unrecognized or improperly treated rupture of the urethra in which stricture will form and subsequent treatment will be necessary. It is noteworthy that these strictures are very firm and intensely resistant to local treatment (dilation by sounds).

Lastly, where primary suture at the time of the injury is impossible due to the extensive fracture of the pelvis. Suprapubic drainage may relieve the situation for a time but severe stricture inevitably results even though a catheter has been used as a splint for the urethra. Perineal dissection done months later in an attempt to free the prostate, excise the stricture and suture the urethra, is not only difficult but very unsatisfactory.

This discussion is primarily concerned with the diagnosis and early treatment of rupture of the urethra, but suggests a method of dealing with the scar tissue occuring as a late complication. This scar has been successfully excised by use of the resectoscope guided under vision through the irregular urethra, straightening it and giving it adequate caliber for the free passage of the urinary stream. No interference with continence has resulted.

No matter when or by whom the cases are seen, traumatic injury to the urethra presents a varying problem to the urologist. In this day of industrialization, rupture of the urethra, while not common, does occur frequently enough for us to stop and review our present concepts as to proper treatment and to discuss new measures that might add to our skill in caring for these unfortunate individuals. Much knowledge regarding care was acquired due to the casualities seen in World War II. Many more cases of severe traumatic injury were seen, treated and evaluated than could be studied in normal peace times.

Human has classified injury to the urethra according to location: 1) pendulous portion, 2) bulbous portion, anterior to triangular ligament; 3) bulbomembranous portion, anterior to triangular ligament; 4) membranoprostatic portion, at or posterior to triangular ligament.

Read at annual meeting, Mid-Atlantic Section, American Urological Association, April 15, 1951.

We can divide injury to the urethra simply as being above or below the triangular ligament.

Kimbrough reported a series of 235 casualties involving genito-urinary injury in the European theater of operation in World War II.

	CASES	PER CENT
Kidney	33	14
Ureter	8	3.4
Bladder	34	14.5
External genitalia	160	68.1

The largest number of injuries occurred in the external genitalia, most of which had accompanying urethral damage. Culp reported 160 cases of wounds of the genito-urinary tract of which 26 or 16.2 per cent were urethral. Fracture of the pelvis was not uncommon with involvement of the bladder. Fracture was the most common complication of urethral injury. Of the 26 injuries to the urethra, 20 were confined to the portion below the urogenital diaphragm. This finding though true in war injuries, does not usually follow in civilian practice.

The injury to the urethra which gives the most disability if not managed properly, is that of complete rupture or partial rupture with fragments of bone tearing the urethra at the apex of the prostate. If one considers the anatomical relations, viz., the fixation at the urogenital diaphragm, it seems obvious why the rupture should occur at this point. Most occur as a result of fracture of the pelvis or subluxation of the symphysis. Lateral compression of the pelvis supposedly causes rupture of the urethra by direct trauma from a bone fragment. Anteroposterior compression may cause separation of the symphysis with resultant tearing or stretching of the urethra.

As one might suspect, trauma to the urethra has as its cardinal symptom, bleeding from the external urethral meatus. This sign seems more likely in injury to the urethra anterior to the urogenital diaphragm. This is true because of the accompanying injury to the corpus spongiosum, a spongy vascular structure. The amount of bleeding has no relation to the extent of the injury. Only a minimal amount of bleeding may mean an extensive injury with separation of the urethra while profuse bleeding might be caused only from a laceration that has not penetrated into the deeper structures and thus does not allow extravasation of blood into the tissues, but causes it to flow freely from the external meatus.

Acute urinary retention is far more common than urinary extravasation. The urethral injury perhaps sets up reflex spasm of the vesical sphincter and the patient is unable to void. The patient with crushing injury to the pelvis who has a desire to urinate but is unable to do so, is almost certain to have a rupture of the urethra rather than a rupture of the bladder. Extravasation of urine usually occurs only when the bladder if unrelieved, finally overflows.

The treatment of urethral injuries should be carried out as early as is practicable. Early treatment should be directed toward control of hemorrhage, shock, diversion of the urinary stream and conservation of tissue. Most of us agree with Uhle and Erb who regard rupture of the urethra as a surgical emergency that should have open repair as soon as possible. Generally speaking, this will be necessary in all suspected injuries to the posterior urethra owing to the high incidence of complete rupture. Even though there is incomplete rupture, the conservative removal of damaged tissue along with evacuation of the hematoma will reduce the risk of fibrosis and liability to stricture formation. Diversion of the urinary stream by suprapubic cystostomy is as important as the initial care of the injured area. Catheterization of the urethra from within the bladder is helpful in the urethral reconstruction. Millin has shown that two or three sutures placed by the retropubic approach, will hold the prostate in position adjacent to the urogenital diaphragm, thus promoting primary healing of the urethra without scar formation.

In general, the passage of a urethral catheter should not be attempted unless facilities for operation are present. Vermooten can see no need for attempting catheterization. He relies on rectal palpation in locating the prostate to determine whether it is elevated and freed from its normal position and a boggy mass substituted in its place.

Even if the prostate can be palpated and found not fixed and able to be pushed upward, this would indicate it has been severed from its attachment to the membranous urethra. If the passage of a catheter is attempted and it fails to reach the bladder, one has no way to be sure that this is not due to an old urethral stricture, spasm of the vesical sphincter or passage of the catheter through an opening in the urethra out into the peri-urethral tissues. A catheter may pass into the perivesical space and allow the return of bloody fluid. This does not necessarily mean the catheter is in the bladder.

Urethrograms can be done early and are a part of the routine in some clinics. Others consider their use a definite loss of valuable time. Urinary extravasation demands immediate radical incision and drainage with adequate diversion of the urinary stream. Delayed treatment increases morbidity and mortality. If treated within twelve hours, the mortality is usually below 20 per cent: after that time it increases rapidly.

If it is agreed that the optimal time for reconstructing the urethra is at the time of the original operation, what measures of closure are used? 1) purse string closure of tears; 2) linear repair; 3) end to end anastomosis over an inlying catheter; 4) traction employing a Foley catheter to pull the apex of prostate down toward the distal urethra (Vermooten-Martin, Reynolds); 5) retropubic suture of the apex of prostate to the membranous urethra (Millin).

Delzell and Stevens showed that a gap in the urethra three-quarters of an inch in length would spontaneously regenerate over an inlying catheter. Culver bridged a two inch gap simply by use of an inlying catheter. DeNicola recently reported the use of a silicone tube, making a permanent replacement of the posterior urethra. It is probable polythene or polyvinyl tubing could be made to serve the same purpose. This might be compared to the operation reported by MacLean and Gerrie with the use of a split thickness skin graft over an inlying catheter to form a new urethra.

Stilbestrol 1 mg. four times daily may be used to reduce postoperative erections until the skin sutures are ready for removal. The urethral catheter is usually not removed for 3 weeks. Sounds should be used cautiously and should progress up to 28F after removal of the urethral catheter.

The advent of newer chemotherapeutic and antibiotic agents has greatly helped combat infection which previously doomed good surgical procedures to failure or delayed sound and rapid healing.

Unoperated cases frequently develop scar tissue which completely occludes the urethra. The following 2 cases are examples. The details of their care and results are reviewed.

CASE REPORTS

Case 1. A man aged 26 was admitted to the hospital June 8, 1950. He complained of marked strangury and the passage of only a few drops of urine for 48 hours.

Eleven weeks previously, he had sustained a fracture of the pelvis with associated injury to the urethra, as evidenced by an inability to void and bleeding from the meatus. A No. 20 Foley catheter had been passed to the bladder and was left in place for 5 weeks, while bed rest was needed for fracture of the pelvis. At the end of that time the catheter drained so poorly that it was removed. No attempt was made to replace it. Voiding was accomplished by straining. It was characterized by a small stream and dribbling. Three weeks before admission, increasing stranguria was noted plus a bearing down sensation in the region of the rectum. Forty-eight hours previously, acute urinary retention developed. Multiple attempts at catheterization and the passage of sounds were made. Some attempts were carried out under general anesthesia. Failing to enter the bladder, his physician asked for consultation. The patient dribbled enough urine to give him some relief while on the way to the hospital.

Examination: The patient was pale and emaciated. Definite suprapubic tenderness and right lower quadrant tenderness were elicited. Spasm of the right psoas muscle caused the right thigh to be partially flexed. The external urethral meatus was traumatized and the edges were edematous. Marked induration along the penile urethra with a definite urethritis accompanied by a yellowish-white urethral discharge was noted. There was marked tenderness on palpation over the right ischium. Rectal examination showed the prostate to be small and far anterior. No masses or tenderness per rectum were noted. The past medical history and systemic review were negative.

Laboratory studies: Hemoglobin—13 gm., red blood cells 4,300,000, white blood cells 13,500. Urinalysis showed numerous red blood cells and pus cells. Urine culture showed E. coli.

A urethrogram (fig. 1) showed that the posterior urethra was tortuous and occluded near the apex of the prostate. There were three sinus tracts, one extending ventrally toward the symphysis and 2 inches in length and clubbed at its extremity. Two smaller tracts were seen leaving the urethra on each side of what appeared to be the main channel. A small amount of medium appeared to escape into the bladder through two small pin point openings well above the expected site of the internal urethral orifice.

Attempts made to pass filiform guides into the urethra were of no avail. Antibiotics were administered.

On June 21, 1950, suprapubic cystostomy with exploration of the bladder neck was carried out. On examination, the internal urethral meatus appeared normal but upon probing the prostatic urethra, *one met a definite impassable curtain* of fibrous tissue. Above the internal meatus, two small dimples were noted that proved to be the openings of sinuses into the periprostatic tissues. Pressure on these tissues caused serosanguinous fluid to escape from the dimpled areas into the bladder. A No. 24 VanBuren sound was introduced into the distal urethra. Upon encountering the curtain of tissue at the apex of the prostate, it was forced through or around the scar tissue and allowed to emerge through the internal urethral orifice. This new channel was thoroughly dilated. A No. 24 Foley catheter was drawn into the bladder. A silk thread was attached to the tip of the Foley catheter and the thread led out of the suprapubic wound, leaving it coiled on the abdomen as the bladder was closed around a No. 24 drainage tube.

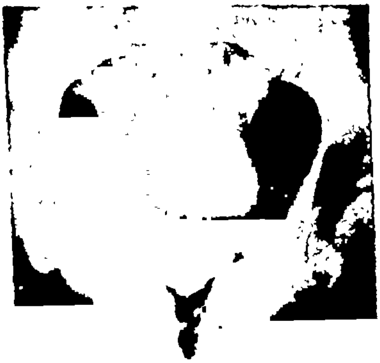

FIG. 1

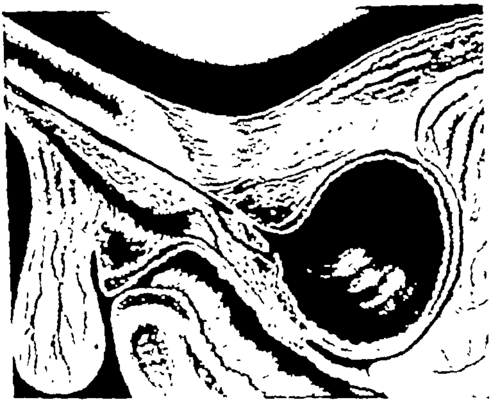

FIG. 2

On July 19, 1950, the urethral catheter was drawn out of the urethra pulling the accompanying silk thread. The thread was attached to the distal end of a resectoscope which was guided by means of this thread into the bladder. Two areas of obstruction were noted (fig. 2). At the bladder neck there was a pocket beneath the bladder floor. This was covered by a flap of mucosa that could produce obstruction. The pocket was unroofed making the internal urethral orifice rather wide. The verumontanum was identified. Distal to the verumontanum, the point where the urethra had been separated at the apex of the prostate was visualized. The distal urethra could be seen ending in a blind pocket ventral and to the right of the new channel. Resection of some of the scar tissue was carried out. The catheter was replaced.

The suprapubic wound healed promptly. The catheter was removed in 10 days. The patient was dismissed from the hospital voiding fairly well. He was seen at weekly intervals during the next three months. Although he was voiding, the stream was not free and sounds were passed with difficulty.

November 16, 1950, the patient was re-admitted to the hospital and evaluation with the resectoscope was carried out. The bladder neck had healed well. However, the dense scar tissue at the apex of the prostate was firm and distorted the contour of the urethra (fig. 3, *A*). The blind pocket at the distal urethra was still noted to be quite evident. Ten or twelve pieces of tissue were removed from the thick scar. Sounds were then found to pass easily and freedom of manipulation of the resectoscope was accomplished (fig. 3, *B*).

The patient has continued to void easily with an excellent stream. Sounds to 28F pass with no evidence of the dense scar tissue being present to obstruct their passage.

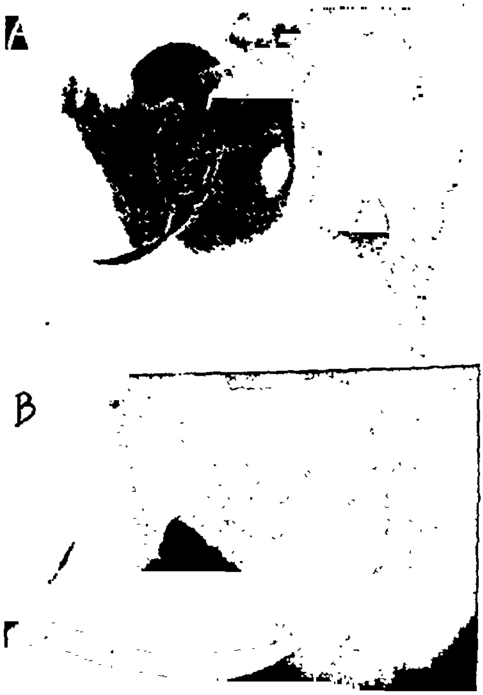

FIG. 3

Case 2. A man aged 24 was admitted to the hospital June 10, 1945 with a history of acute urinary retention for 24 hours. He gave a history of having been thrown from an automobile (Jeep) while in the Army and sustaining a fracture of the pelvis. His urethra was treated by catheter splint for 3 weeks. After the pelvic lesions healed, he was dismissed from the hospital and soon discharged from the Service. Three months later acute urinary retention developed.

Examination showed a well developed and nourished adult male. The bladder was distended to the umbilicus; the prostate was normal size.

Laboratory studies were within normal limits.

The patient was taken to the operating room. Filiform guides were passed through a tortuous, scarred urethra. The urethra was dilated to admit a No. 24 resectoscope. A dense scar of the urethra at the apex of the prostate was noted, where it distorted and angulated the urethra at this point. This hard, firm tissue was removed. Sounds were passed freely following this procedure. The patient has continued to void freely and the urine has remained crystal clear.

SUMMARY

The common complication of dense stricture formation with rupture of the urethra is discussed.

The severity of the initial injury is often an unreliable sign as to the degree of trauma since intractable strictures often occur where the initial signs are suggestive of only mild injury.

A definite fracture in the pubic region, often crushing injuries, lends support to the presumption of posterior urethral injury. Decision must be made then whether immediate exploration is advisable. In most cases it is wise.

The prevention of serious complications with urethral rupture is greatly dependent on early diagnosis and efficient treatment. The late complications result from infection and fibrosis and often are serious enough to produce complete and fairly sudden urinary retention.

Late urethral repairs mean increased morbidity and difficult surgery.

The resectoscope has been used successfully to remove the dense scar tissue of these strictures. We believe it can be used often in others where this complication has been allowed to occur. In spite of the fact that the resection of the scar tissue was carried out at the apex of the prostate, no incontinence resulted.

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URETHRAL STRICTURE: A STUDY OF 227 CASES*

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Urethral stricture is gradually disappearing from the urological scene and it is safe to assume that within the span of less than another generation it will become quite rare. The recognition that the use of powerful antiseptics in the treatment of gonococcal urethritis was responsible for the tendency to the stricture formation, and its abandonment for milder local measures was an important factor in the reduction of the incidence of stricture. With the advent of chemotherapy and antibiotics, gonococcal urethritis, once a terror to both the patient and the urologist, because of the uncertainty of its course, its complications, and the unreliability of the cure criteria, became a short-lived mild infection, and the incidence of stricture formation was further reduced.

Urethral stricture, however, still remains a live urological problem, chiefly because a great many patients come under observation many years after the initial infection. In this series, in the group which gave a history of gonococcal infection, the average length of time before the patient was examined was 13.9 years, while in a group of 66 cases the initial lesion antedated examination by 20 to 58 years.

ETIOLOGY

In this series there were 191 males and 36 females. Antecedent history of gonococcal infection was obtained in 73.8 per cent in the male group; it is possible that some patients may have concealed it. The etiological factors may be grouped as follows: Gonococcal urethritis, 143 (3 in women patients); nonspecific urethritis, 3; tuberculous urethritis, 1; urethral injection of carbolic acid preparations by patient to avoid military service, 2; congenital, 11; trauma, 5; prostatectomy, 8; transurethral resection, 1; etiology not ascertained, 53 (32 in women).

The patient with tuberculous urethritis, an extremely rare condition, indeed, was a boy 16 years of age, who was seen in a pre-uremic state. His urine was laden with pus and tubercle bacilli and his urethra did not admit the finest filiform bougie. Inadequate neutralization of carbolized urological instruments may result in marked exfoliative urethritis and eventual stricture formation.

PATHOLOGY

It is not the intention of this paper to delve extensively into the local pathology of urethral strictures, as the writer is mostly concerned with its management and with the various complications which may arise from urethral instrumentation. In this series the upper urinary tract lesions must have been missed more often prior to advent of excretory urography, and even a plain x-ray was not taken in a surprisingly large number of cases. Many of the patients who reported for periodic dilatation were of the transient type, and did not desire a thorough urological study. On the other hand, in a number of earlier patients with acute bladder retention or other complications, we were so concerned with the urgent aspect of the case, that the x-ray examination was deferred or, in some cases, entirely overlooked. The writer,[1] in collaboration with Dr. A. A. Solomon, reported 22.6 per cent of upper urinary tract lithiasis in a group of urethral stricture cases in which x-rays were taken; as of this date, x-ray studies were made in 154 patients, and upper urinary lithiasis was found in 32 cases (15 kidney and 17 ureteral stones), or 20.8 per cent. Including other lesions, such as hydronephrosis, renal infections, hydro-ureter and ureteral stricture, the incidence was 26.8 per cent. It is difficult to state what would be the real frequency of upper urinary lesions had all the cases in this series been subjected to x-ray workup.

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Associated lower urinary tract infections were present in 22 per cent. The incidence of urethral fever following instrumentation was much higher in infected cases before the sulfa drug-antibiotic era, and rendered the management of urethral strictures more difficult. In 6 cases peri-urethral abscesses complicated the condition, while marked urinary extravasation involving the penis, the scrotum and the lower abdominal wall occurred in 2 patients having strictures in the anterior urethra. The foregoing complications are undoubtedly higher in hospital ward practice.

Of other associated lesions in the lower urinary and genital tracts, it is important to mention that there were only 4 cases of vesical calculi (1 in a woman with a filiform stricture), 4 cases of urethral calculi, 9 cases of prostatic adenoma and median bar and 34 cases of marked chronic prostatitis and seminal vesiculitis.

According to location, the distribution in male patients was as follows:

	Cases
Anterior urethra	46
Bulbomembranous urethra	121
Anterior and bulbomembranous urethra	4
Prostatic urethra (mostly post-prostatectomy)	12
Location undetermined (history of stricture, not instrumented by writer)	8

CALIBER OF STRICTURES

For reasons stated later the caliber of the stricture was not accurately ascertained in many cases. The presence of the filiform type of stricture, however, was definitely established in 65 patients, 2 of whom were women. Strictures ranging anywhere from 8 to 20F were found in 133 cases. The caliber of strictures was larger in women, and the diagnostic criterion in a good many cases in the female group was based on marked improvement of long continued symptoms of bladder distress following the introduction of a cystoscope.

SYMPTOMATOLOGY

This depends upon the following factors: 1) associated infection of the lower urinary and genital tracts; 2) the extent of urinary retention; 3) associated lesions of the urinary tract above the stricture; 4) the willingness of the patient to undergo periodic dilatation.

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[1] Dourmashkin, R. L. and Solomon, A. A.: J. Urol., 48: 196, 1942.

Probably the earliest and most constant manifestation is narrowing of the stream and difficulty in starting the urinary flow. Diurnal frequency, nocturia, dysuria, urgency were more marked when they were associated with lower urinary tract infection. In a number of cases there was a remarkable spontaneous disappearance of the infection shortly after dilatation of the stricture. Nocturia, which in many cases suggested the presence of prostatic enlargement, was present in 76 patients, many of whom had neither infection nor evidence of bladder retention. It is safe to assume, however, that nocturia is not at all as constant a symptom in urethral stricture as in prostatic obstruction. Thirty-seven patients were seen during an acute attack of bladder retention. As contrasted to bladder retention resulting from prostatic obstruction, the condition was permanently relieved in the greatest majority of cases by periodic urethral dilatation. Hematuria, frequently a knotty problem from the point of view of differential diagnosis, was present in 39 cases, of which only 11 patients had upper urinary tract lesions, prostatic adenoma and carcinoma. In 14 patients, the lesions in the upper urinary tract, some of them far advanced, were of the silent type, the condition being discovered in the course of the routine urological investigation.

TREATMENT

In this series, 5 deaths were directly attributable to urethral instrumentation. It should be borne constantly in mind that the fibrous tissues in the strictured area are richly supplied with blood vessels and that instrumentation carried with undue force causes a break in the blood vessels more readily than in a normal urethra. Urethral fever is due to sudden invasion of blood by bacteria which enters the circulation through the traumatized areas. In 1902, Bertelsmann and Mau[2] described 3 cases of urethral fever following urethral instrumentation in which positive blood cultures were found. In 1916, Crabtree[3] reported 7 cases having positive blood cultures after urethral catheterization. In 1929, Scott[4] reported 82 cases of blood stream infection in urology of which 81 cases occurred in conditions in the lower urinary tract. In 34 cases positive blood cultures were obtained between 5 and 12 hours. The urethra was the probable portal of entry in 80 per cent of the cases.

The occurrence of excessive bleeding, in itself a useful diagnostic point, during an attempt at passing a catheter or a cystoscope into the bladder in cases in which the presence of a stricture is not known, and which are not associated with prostatic obstruction, should put one immediately on guard against further forcible instrumentation. Urethral fever will rarely occur if bleeding does not take place. The basis for management of urethral stricture should be the effort to minimize the incidence of bleeding, and for this reason metallic instruments, either for measurement or early dilatation, should not be used. There is a urological device which should merit the admiration and daily blessing of every urologist, the Philip's filiform bougie and follow catheter. It eliminates undue trauma and minimizes the incidence of urethral fever. It enables one to empty a bladder in cases of acute retention where others have repeatedly failed. The device was employed in practically every case in this series, once the presence of a stricture was recognized. Six patients in this series had previous external urethrotomies, one had internal urethrotomy, yet in all of them I was able to dilate the stricture with Philip's device. I failed to pass by the obstruction only in 7 patients, all of whom were operated upon. Five of these patients had strictures in the bulbomembranous portion of the urethra. They were seen in the early years of my practice and were subjected to external urethrotomy. The operation was urgent in 3 patients because of acute bladder retention. Subrapubic cystotomy with retrograde dilatation of urethra was performed in 2 cases of post-prostatectomy stricture, in one of which operation was necessary anyway because of large bladder calculi. The operative incidence in uncomplicated cases was only 3 per cent. The urethrotome for anterior stricture, in my opinion, should be relegated to the museum of urological antiques. I always believed that internal urethrotomy is a cruel and unnecessary procedure and it was never used in this series. As Hyman[5] aptly stated, urethrotomy, whether internal or external, adds trauma to an already injured urethra and every incision causes additional scar tissue.

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[2] Bertelsmann and Mau: Munchen. Med. Wchnschr., **49**: 521 1902.
[3] Crabtree, E. G.: Lancet clinic, Cincinnati, **115**: 96, 1916.
[4] Scott, W. W.: J. Urol., **21**: 527, 1929.

I was not able to pass the filiform bougie by the stricture during the first attempt in 20 patients. Even a filiform bougie may produce excessive bleeding and the manipulation should not be unduly prolonged. The procedure was repeated in a day or two until, after two or three attempts, the obstruction was passed in all cases. When a straight filiform cannot pass through, it is remarkable how easily a corkscrew filiform, which is made by winding the distal end of the bougie around a thin pencil, will do the trick at the same sitting. Occasionally it was possible to slip by an opening in the strictured area by introducing several filiform bougies into the urethra. On very rare occasions, in deep urethral strictures, a natural curved silk woven catheter and even a small sized metallic sound could be introduced when the filiform bougies failed. I have always questioned the accuracy of diagnosis in these cases; one of these patients had a definite associated vesical neck obstruction and prostatic calculi.

Once the filiform bougie enters the bladder, the choice of the size of the follow-up catheter depends upon the amount of resistance and bleeding encountered. Usually it is well to be contented with a number 14F catheter, although in some instances I was bold enough to start with a 16F and even with an 18F catheter. As a rule, I leave the catheter indwelling for one-half to one hour. Because of fear of urethral fever, acute urethritis and epididymitis, especially in the era antecedent to introduction of sulfa drug and antibiotics, the catheter was left indwelling for any extensive time only in a few instances. Occasionally, in cases not accompanied by bleeding, I would reinsert a larger catheter during the first treatment. The dilatation would be carried out once a week with the Philip's catheter until 20 to 24F. A shift was then made to metallic sounds, straight or curved, according to the site of the stricture, and the urethra was gradually dilated to 26–28F. The Kollman dilator was practically never used in male patients, but in the female, whose stricture, as a rule, was of larger caliber, it was the instrument of choice. Lazarus[6] suggested the use of diathermy applied to a metallic sound, and this method was found to be of distinct value in 6 cases which would not allow larger sounds.

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[5] Hyman, A.: Am. J. Surg., 39: 152, 1925.

The patient was instructed to report twice a year for urethral dilatation for the rest of his life. Unless the importance of periodic dilatation is explained in great detail to the patient, a well dilated stricture may be reduced even to a filiform status within an amazingly short time. There are stubborn, dense, usually traumatic strictures, which will never admit a curved metallic sound and will not allow more than 20–22F dilatation with the Philip's catheter. These cases should be seen oftener. In this series there is a large group of patients who came under observation many years ago with marked symptoms of urinary distress, bladder retention and urinary tract infection who have been rendered entirely symptomless by their strict adherence to the rule of periodic dilatation.

Two per cent procaine solution was used for local anesthesia. Undue pressure by penile clamp may frequently cause bleeding even in a normal urethra. To avoid contact of urine with a bleeding urethra the patient was instructed not to void for at least two hours after instrumentation; often this was not possible. After the introduction of chemotherapy, sulfa drug was given one day prior and two days after the instrumentation. Later this was supplemented by injection of 300,000 to 600,000 units of penicillin. The reduction of the incidence of urethral fever was, indeed, remarkable.

The patient's general health, the status of the circulatory system, blood chemistry, and renal function should be well known to one who is called upon to treat the urethral stricture. Lesions in the upper urinary tract amenable to correction either by open surgery or by transurethral route, must not be allowed to remain untreated too long. In 17 cases of ureteral calculi in this series, 15 were made to pass the stone by cystoscopic manipulations, after preliminary urethral dilatation.

COMPLICATIONS ARISING FROM URETHRAL INSTRUMENTATION

Urethral fever. This condition followed instrumentation of strictures in 23.5 per cent of cases in this series in the pre-sulfa-antibiotic era. The patient would have a chill of varying intensity and fever within 12 hours. The fever in some cases would go up to 106F, remain for 3 to 7 days, and gradually recede. In 2 earlier cases the condition was fulminating in character and resulted in the death of the patient. These patients were not instrumented by the writer but were seen by him in consultation. In one case marked bleeding occurred following the passage of a metallic sound; in the other patient chills and fever occurred within 24 hours following the introduction of an indwelling catheter. The occurrence of urethral fever was unpredictable in those days and would plague both the patient and the urologist even after the gentlest manipulation. Some patients considered the onset of chills and fever as a routine, inevitable occurrence and they would arrange to take time off to weather it; other patients refused to submit to further treatment and allowed the condition to progress until extreme urinary distress would bring them back.

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[6] Lazarus, J. A.: J. Urol., 45: 229, 1941.

With the use of chemotherapy and antibiotics the incidence of urinary fever has dropped almost 400 per cent. In 87 cases thus treated urethral fever developed in only 5 patients or 5.7 per cent. The course of chills and fever was, as a rule, mild, and there were no instances of mortality.

Urohepatic syndrome. This condition was described for the first time by the writer[7] in 1928. It was applied to 2 cases of fatal cholemia following instrumentation of urethral stricture having co-existing hepatic cirrhosis. In 1 patient the diagnosis was confirmed by necropsy. The other reported case was a patient who had hepatic cirrhosis and who developed mild jaundice following cystoscopic manipulation for ureteral calculus; this patient passed the stone and recovered. After the article was submitted for publication, the late Dr. Roy B. Henline[8] related to me a case of anuria and deep jaundice occurring in a patient immediately following the passage of a sound for dilatation of urethral stricture. In 1929 Fitz-Hugh[9] reported 4 cases of hepato-urological syndrome, and since my original report, a large literature has grown up on various aspects of relationship between liver and urinary tract disease which was ably compiled by Wilensky.[10]

Colloidal silver embolism. Argyria, a permanent, peculiar, ghastly ivory-blue, or slate colored pigmentation of the skin, with a dark-blue line on the edges of the gums, has been described following protracted use of silver salts for urethritis, cystitis, or mucous membrane lesions elsewhere in the body. In looking over the literature, however, I have not come across a case of an embolism due to the use of colloidal silver solutions. The following are 2 such cases which resulted in sudden death:

B. T., a man, 31 years old, was seen on May 29, 1931. He gave a history of recurrent attacks of gonococcal urethritis. A filiform obstruction was encountered at midurethra, and there was considerable bleeding on manipulation. A 10 per cent colloidal silver solution was injected with considerable pressure because of the resistance encountered in the urethral passage. On the way home, in the subway, he felt nauseous, and when he arrived home he became suddenly dyspneic, cyanosed, and died 2 hours after treatment. I learned of his death a few days later and the description of his symptoms by his family physician pointed to a pulmonary embolism. The autopsy disclosed no lesion anywhere, but in my discussion with the medical examiner I gathered the impression that a colloidal embolism was not suspected.

A few months later Dr. H. Weinberg,[11] assistant medical examiner of New York City, related to me a case of a sudden death of a young man whose urethra was treated with colloidal silver preparations. On autopsy colloidal silver emboli were found in blood vessels.

Since then I have never used colloidal silver solutions on any bleeding area of the urinary tract.

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[7] Dourmashkin, R. L.: J. A. M. A., 90: 908, 1928.
[8] Henline, R. B.: Personal communication.
[9] Fitz-Hugh, T. Jr.: Med. Clinics of North Amer., 1929 (Jan.) p. 1101.
[10] Wilensky, A. O.: Arch. Surg., 38: 625–691, 1939.
[11] Weinberg, E.: Personal communication.

Untoward results from local anesthesia. In two instances patients went into a state of semishock following installation of 2 per cent procaine solution into the urethra. Undoubtedly there was a rapid absorption of the drug into the circulation due to a break in the blood vessels.

Acute urethritis and epididymitis. There was a recurrence of gonococcal urethritis in 3 patients who gave a history of infection many years ago. In this series there was an amazingly low incidence of epididymitis following instrumentation, only 1 case, undoubtedly due to my reluctance to use indwelling catheters for any considerable lengths of time.

False passage. None was encountered in this series.

DIFFERENTIAL DIAGNOSIS

There are 3 conditions in which an error in diagnosis can be readily made: 1) Prostatic hypertrophy and median bar; 2) deep urethral calculi; 3) lesions accompanied by hematuria.

1) Prostatic hypertrophy and median bar. In this series 8 cases of prostatic adenoma and 1 case of median bar were encountered. In 2 of these cases the presence of urethral stricture, one involving the anterior urethra, and the other the bulbomembranous portion, had not been previously recognized. These patients came under observation with post-prostatectomy suprapubic fistulas which closed promptly following urethral dilatation supplemented by indwelling catheters. The following are the criteria which should clarify the diagnosis:

a) Rectal palpation: The presence of an enlarged median or anterior prostatic lobe cannot be detected by this method, but lateral lobe enlargement should be ordinarily made out.

b) Retrograde and intravenous cystograms show definite elevation of the floor of the bladder in obstructive vesical neck lesions.

c) Residual urine, which is found in a small group of stricture cases, especially in patients giving a history of repeated attacks of acute bladder retention is, as a rule, completely reduced after adequate urethral dilatation, while it remains constant in prostatic obstruction.

d) Measurements of the catheter at the point it draws urine, showing no elongation of the urethra, should point to a stricture.

e) In filiform strictures involving the deep urethra one frequently encounters a cartilagenous resistance.

f) Urethrograms, preferably made with 20 per cent methiodal sodium, are helpful, but they were seldom used in this series.

g) Cysto-urethroscope, when it can be introduced through the strictured areas and passed without producing bleeding, reveals the most accurate diagnostic picture of obstructive lesions at the vesical neck and prostatic urethra.

2) Deep urethral calculi. These may be easily overlooked, not only because of the failure by even an experienced urologist to take a plain x-ray in cases of stricture for the foregoing reasons, but also because of failure to include the bulbomembranous portion of the urethra on the x-ray. A scratch mark elicited on a wax tip bougie, passed to the point of obstruction, should prove the presence of a stone beyond any doubt. Grating is not diagnostic, as the same can be elicited in tight, dense, fibrous strictures. I have encountered 21 cases of urethral calculi, 4 of which were associated with bulbomembranous strictures. One of these (courtesy of Dr. A. A. Solomon) had an old traumatic stricture with marked infection of the lower urinary tract. He was treated for many years by several urologists, but the presence of a stone, 8 by 8 mm. was not recognized because an x-ray was not taken. He passed the stone shortly after a large sound was introduced under general anesthesia to the point of obstruction. The stricture was dilated and his symptoms. as well as the infection, completely subsided. In the second case, the stone, 6 by 10 mm., was removed by Young ronguer after it was pushed into the bladder by a sound. The third patient had a suprapubic cystotomy because the stone was too large, while the fourth patient was lost from observation.

3) *Lesions, other than urethral strictures, accompanied by hematuria.* In the greatest majority of cases in this series hematuria was caused by urethral stricture itself and was not associated with other lesions in the urinary tract. There are cases, however, which demand an immediate and accurate determination of the source of bleeding. To this group belong cases with massive hematuria in which it is important not only to make an accurate diagnosis, but also to make an attempt to check the bleeding by transurethral route. In tight filiform strictures it was often impossible to dilate the urethra adequately in order to introduce even a small caliber cystoscope. This brings us to the consideration of the cystoscopic filiform attachment.

THE VALUE OF CYSTOSCOPIC FILIFORM ATTACHMENT

The device was described by Frontz[12] and it consists of a distal cystoscopic cap with a male screw, to which a filiform bougie can be threaded (fig. 1). Subsequently Malisoff[13] emphasized the importance of its use. The device has been of immense value in this series, and, I believe, it ought to be an integral part of every cystoscopic set. It can be supplied, however, by the American Cystoscope Makers, Inc., for any type of cystoscope. The diagnostic value in cases which apparently did not lend themselves to accurate evaluation was superb, but it is in the field of emergency cystoscopic investigation and treatment that its use was, indeed, dramatic in a number of instances.

In one patient the family physician passed a bougie by a filiform stricture in the bulbomembranous urethra. A large fragment of the bougie broke off and remained in the bladder. The patient was admitted to my service at Fordham Hospital and I was able to remove the bougie with the aid of the Frontz device screwed into a 21F operating cystoscope. In another typical case of marked hematuria, associated with a filiform stricture in the bulbomembranous urethra, an exploratory cystotomy was contemplated because the cystogram pointed to the possibility of a bladder neoplasm, but the filiform bougie cystoscope ruled it out, the bleeding being due to the stricture. Another patient with filiform stricture in bulbomembranous urethra developed marked hematuria. The diagnosis, checking of hemorrhage and eventual destruction of a large bleeding benign papilloma by fulguration was made possible by the Frontz device. In still another case its use unquestionably saved the patient's life; he had a filiform bulbomembranous stricture and came under observation with complete anuria due to bilateral calculous obstruction of the ureter. Kidney drainage was reestablished by ureteral catheterization and the patient eventually passed a small stone from the right ureter; the stone on the left side was too large and too high. Operation was advised which the patient refused. The Frontz device was used routinely in a number of difficult cases to differentiate a stricture from prostatic enlargement.

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[12] Frontz, W. A.: Presentation of device facilitating the introduction of the cytoscope in certain difficult cases. J. Urol., 2: 39, 1918.

[13] Malisoff, S.: Urol. & Cutan. Rev., 41: 619. 1937.

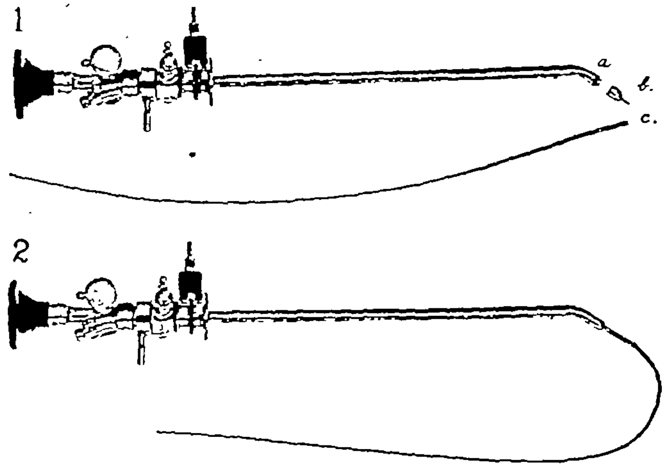

FIG. 1. *1*, Frontz cystoscopic filiform device. *a*, 21F Brown-Buerger cystoscope from which ordinary cap is unscrewed at distal end. *b*, cap with male screw for *c*, filiform bougie. *2*, Frontz cystoscopic filiform device assembled.

SUMMARY

Upper urinary tract lesions were found in 26.8 per cent of cases in which x-ray studies were made in this series. In 21.7 per cent there were stones in ureter and kidney.

The routine x-ray of the urinary tract should include the deep urethra for a possibility of a urethral stone.

The basis for management of urethral strictures should be aimed at minimizing the incidence of urethral bleeding, and for this reason metallic instruments either for the measurement or early treatment, should be avoided. Philip's filiform bougie and follow catheters, without leaving them indwelling, were used in the early phases of treatment and followed by dilatation with metallic sounds.

There were 5 external urethrotomies in this series and 2 suprapubic cystotomies with retrograde dilatation, one of which had large bladder calculi, an operative incidence of only 3 per cent. Internal urethrotomy should be discarded.

There were 5 deaths in this series directly attributable to urethral instrumentation.

The incidence of urethral fever was 23.5 per cent in the era preceding chemotherapy and antibiotics, and only 5.7 per cent when the latter were given routinely before and after instrumentation.

Urohepatic syndrome and colloidal silver embolism are among the rarer complications resulting from instrumentation and should be guarded against.

A cystoscope with a filiform bougie attachment is an extremely valuable aid in differential diagnosis and transurethral treatment of conditions above the strictured urethra.

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CO-EXISTENCE OF CONGENITAL MEDIAN BAR AND URETHRAL VALVES

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Congenital obstructions of the bladder neck in the infant are known entities and are seen from time to time. One finds posterior urethral valves in one and median bars in another. We encountered both these pathological congenital obstructions in the same infant. This double hurdle obstruction caused complete destruction of both upper urinary tracts with death shortly after birth.

CASE REPORT

W. C., a newborn Negro, died on February 27, 1951, fifteen days after birth. Delivery had been normal. The first examination the day following admission revealed no physical abnormalities. On the third day it was noted that the baby looked quite dry, had lost 10 ounces in weight. Clysis was given. Ten days post-delivery it was noted that the baby's abdomen was distended, and that the baby was dribbling urine throughout the day. An x-ray of the abdomen revealed a large soft tissue mass which was reported as possibly being a full bladder. Catheterization yielded 100 cc clear urine. Three hours later the abdomen was again distended; catheterization was accomplished without difficulty, and 110 cc more urine was obtained. The catheter was left indwelling, and terramycin was started. The following day an intramuscular urogram revealed no opaque medium in the kidneys after 1½ hours. The following day a cystogram revealed an obstruction at the vesical neck and another obstruction at the bulbomembranous portion of the urethra. There was no reflux of dye into the ureters. The baby's general condition gradually grew worse. It was vomiting its feedings and was therefore put back on clysis. The child expired the next day.

Intramuscular urography failed to visualize any part of the urinary tract because of extremely low renal function. A cystogram made with diodrast showed a comparatively large, round bladder (fig. 1, *A*). After removal of the catheter another picture was taken. This film revealed a completely rounded bladder base with some overflow into the posterior urethra (fig. 1, *B*). One notes a thin line of diodrast leaving the bladder and entering into a rounded pouch of the posterior urethra. A third film taken a few minutes later revealed the bladder with the rounded base completely cut off from the urethral pouch which appeared at this stage as a separate shadow away and below the bladder.

Autopsy findings (figs. 2 and 3): No gross changes or congenital abnormality could be observed. The pathological changes were confined entirely to the urinary tract. Both kidneys were mere shells and markedly dilated. Both ureters were dilated, thinned out and tortuous. The bladder was larger than normal and markedly thickened. The bladder wall measured about ½ cm. The musculature was heavily trabeculated forming prominent rugae on the mucosal surface.

Both ureteral orifices were properly placed and patent. The trigone was notably thickened. A heavy, broad and hard median bar was present at the bladder neck.

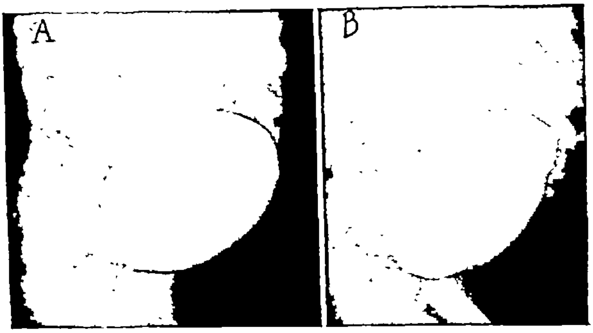

Fig. 1. *A*, cystogram showing round bladder base, thinned out bladder outlet and roomy posterior urethral pouch. *B*, cystogram showing complete separation of bladder from the posterior urethral pouch caused by the intervening median bar.

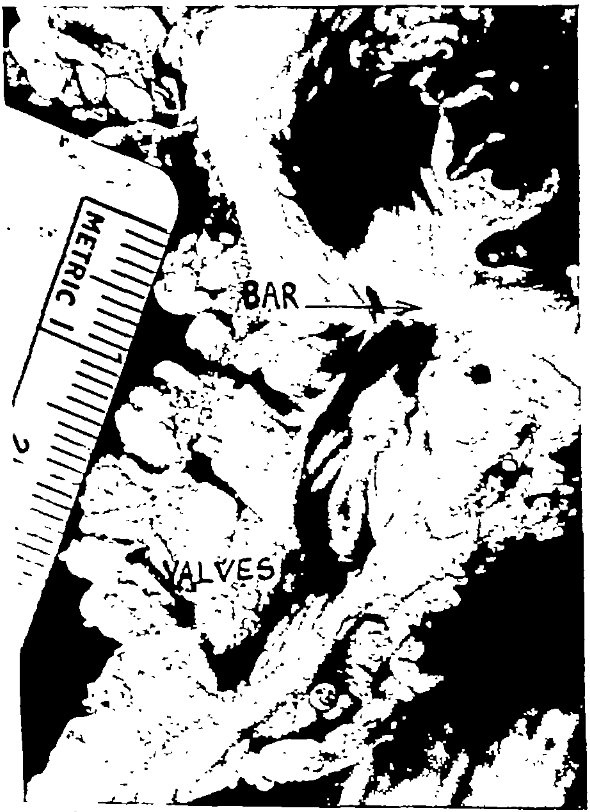

Fig. 2. Close-up view of bladder neck. Arrows indicate median bar and valves. Note roomy posterior urethral pouch, large verumontanum and ridges.

On leaving the bladder there was a sheer declivity down along the bar. The posterior urethra was very large, forming a regular chamber, measuring 2 by

1 by 1 cm. The verumontanum was about the size of an adult organ with thick ridged cristae downward to the bottom of the chamber, where it divided into right and left, forming a large and broad valve on either side. The anterior urethra appeared normal. The remainder of the genital tract showed normal development.

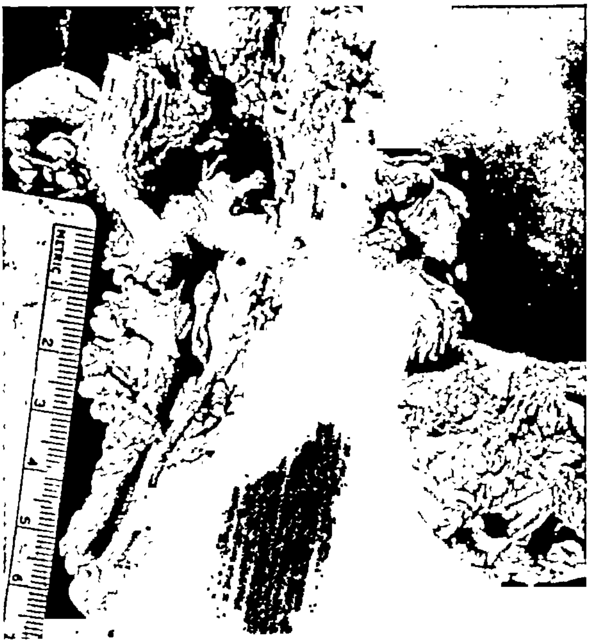

FIG. 3. Entire specimen of bladder with complete destruction of the kidneys and ureters.

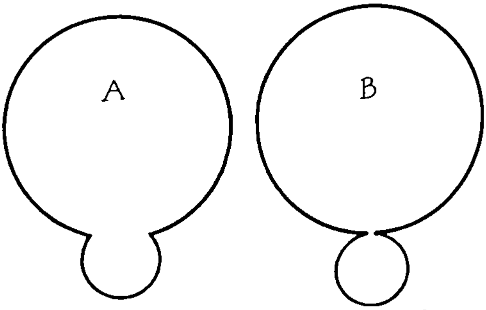

FIG. 4. Schematic representation of bladder neck shadow by cystogram. *A*, in valves only. *B*, case of combined bar and valves.

COMMENT

The cystogram and urethrogram (fig. 4) clearly define the actual changes found at autopsy. The sharp cut-off below the bladder between its rounded base and the special urethral chamber was caused by the intervening thick and hard median bar. This urethral chamber is therefore bound by the bar above and the valves below. This unusual condition was probably completely developed in utero and caused complete destruction of both kidneys before birth. In order to cause such massive destruction of the upper urinary tract by back pressure, one must assume active voiding into the amniotic sac for a long period of time. One can assume that voiding occurs from the date of establishment of renal function which occurs approximately at three to four months.

Should a case such as this come to surgery right after birth a correct and detailed diagnosis is extremely important in actually removing both obstructive factors. At open cystotomy a bar would be seen and could be accepted as the only existing obstruction. By removing the bar one would acquiesce and fail to look for another equally obstructing pathological factor. It is suggested that in every case of congenital median bar a careful search be made for the co-existence of posterior urethral valves.

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TREATMENT OF CARCINOMA OF THE PROSTATE BY INTERSTITIAL RADIATION WITH RADIO-ACTIVE GOLD (Au198): A PRELIMINARY REPORT

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Patients with carcinoma of the prostate may be divided into three groups depending upon the extent of the lesion. In the first group the lesion is completely confined to the prostate. There is usually no evidence of bladder neck obstruction, the lesion is not fixed, there are no evident metastases and the blood acid phosphatase is normal. Radical prostatectomy is usually considered the treatment of choice in this group which comprises 5 to 10 per cent of all patients with carcinoma of the prostate (Thompson, Creevy, Jewett, Young, and Smith).

In the second group, comprising 55 per cent of the total, the neoplasm has spread beyond the confines of the prostate and usually presents the following: bladder neck obstruction and local extension through the capsule into the periprostatic, perivesical and perivesicular tissues and spread to the regional lymph nodes. Such a lesion can be removed only by viscerectomy. Since this procedure rarely accomplishes complete removal of the involved lymphatics and these patients average over 70 years of age, viscerectomy is rarely indicated. In the majority of such cases the therapy has consisted of transurethral resection to relieve obstruction and hormonal therapy (orchiectomy, estrogen) for palliation.

Those in the third group, which comprise 30 to 65 per cent of all cases, have local lesions similar to those in group 2, but in addition have distant metastases. The therapy for these patients has been similar to that in group 2. A short course of roentgen therapy to the painful bony lesions at times has been of value where hormonal therapy has failed.

BACKGROUND

Is it possible to achieve in group 2 what may be accomplished in group 1 by radical prostatectomy? Viscerectomy is being tried, but is applicable (in the authors' opinion) for a very few of these patients. The hormonal attack, thus far, has produced only palliation.

Radiation with radium and roentgen rays has been used as a third method of therapy. The first curative attempts by radiation were made by Pasteau and his collaborators. These were soon followed by Young, Barringer, Deming, Bugbee Bumpus, and others. Interstitial radiation with radium and radon and contact therapy with radium or external radiation alone or in combination with other methods were tried. At times striking reduction in the mass of the tumor was observed, and several cases were apparently cured. The report of Deming, which analyzed 100 cases treated by radiation, showed definitely that, given intensive radiation, most of these tumors responded to some extent. However, with

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Read at annual meeting, North Central Section, American Urological Association, Toledo, O., October 5, 1951.

intensive radiation, complications resulted from the effect upon the surrounding tissues. Severe bowel and bladder irritation and ulcerations developed. Because of these complications, the necessary massive dosage could not be delivered.

By utilizing certain of the radio-active isotopes it is possible to give more localized and intensive radiation. Radioactive gold (Au198) in colloidal solution is apparently nontoxic and will remain for the most part (90 per cent) at the site of the injection when instilled into tissue. Its half life is 2.7 days and about 90 per cent of the energy released is in the form of beta radiation with a maximum range of 3 mm. in tissue. This means that intensive radiation occurs only in the immediate area around foci of the isotope and does not extend more than a few millimeters beyond this point. Thus it seems possible by direct infiltration of radio-active gold sol to give a cancerocidal dose of radiation and still circumvent most of the objectionable side complications in the rectum and bladder associated with radium, radon and roentgen therapy. About 97 per cent of the radiation is delivered over a period of 1½ weeks and instead of originating from ten to fifteen sources, the colloidal gold sets up literally billions of point sources of highly ionizing beta radiation. The work of Allen, Bonebrake and their group at Washington University, St. Louis, in which they inject the sol into the parametrium, indicates that enough radio-active material is taken up by the lymphatics and delivered to the regional lymph nodes so that metastatic neoplasm in these nodes is affected. These features of radio-active gold seem desirable for the treatment of prostatic cancer. The suprapubic approach makes it possible to expose the prostate, the lymphatics about the rectum, the regional lymph nodes and the seminal vesicles and adjacent lymphatics so that visualized or palpable tumor can be thoroughly infiltrated with the radio-active material. Since the total volume of the carcinoma is relative small (rarely over 150 cc), it is possible to give massive doses of radiation to the tumor tissue and, at the same time, keep the total dose small. The layers of fascia about the prostate and seminal vesicles with their vessels and lymphatics form a fascial compartment about these structures, and this aids in holding the radio-active solution in the desired location. All of these factors make the treatment of carcinoma of the prostate by interstitial radiation with a radio-active isotope such as Au198 seem very promising.

MATERIALS AND METHODS

This report concerns the first twenty cases that were treated by interstitial radiation with Au198. All of these cases belong in group 2. However, there was considerable variation among them with regard to the quantitative involvement of the prostate, periprostatic tissues and regional lymphatics. Histologic proof of carcinoma was obtained in each instance either by perineal punch biopsy or transurethral resection.

The technique of administration of the radio-active gold involved three basic problems: first, the dosage per cubic centimeter of involved tissue; second, adequate distribution within the carcinoma and lymphatics; and third, protection against radiation hazards (fig. 1).

It is not possible at this stage of our experience to state what dose is most efficacious. We have cautiously increased our dose from one that we now believe was too small to a dose that is probably unnecessarily large. This range has varied from 0.3 millicurie to 3.5 millicurie per estimated cubic centimeter of involved tissue. While the gamma component of the radiation is of little importance in small masses of 25 grams or less, it becomes increasingly more important as the size of the mass increases. Thus, in small glands we feel safe in injecting 3 millicurie per cubic centimeter of tissue, but in large glands weighing over 150 grams, our dose decreases to 1 millicurie per cc or even less. The maximal dose used so far has been 160 millicurie. A fear of the results of total body radiation and of liver and spleen concentrations, especially when hyaluronidase is added to the solution, has caused us to be cautious about exceeding this arbitrary dose. Daily monitoring of the patients has failed to detect any appreciable accumulation of gold in liver, spleen or lungs, but counts taken over the pubic area suggest that there is some loss of gold from the prostatic area. This is not accounted for by loss in the urine (which contains only minute traces of activity after 48 hours), nor in the feces, which are always inactive. In light of this, supplemented by the results of animal experimentation, we believe that some gold must enter

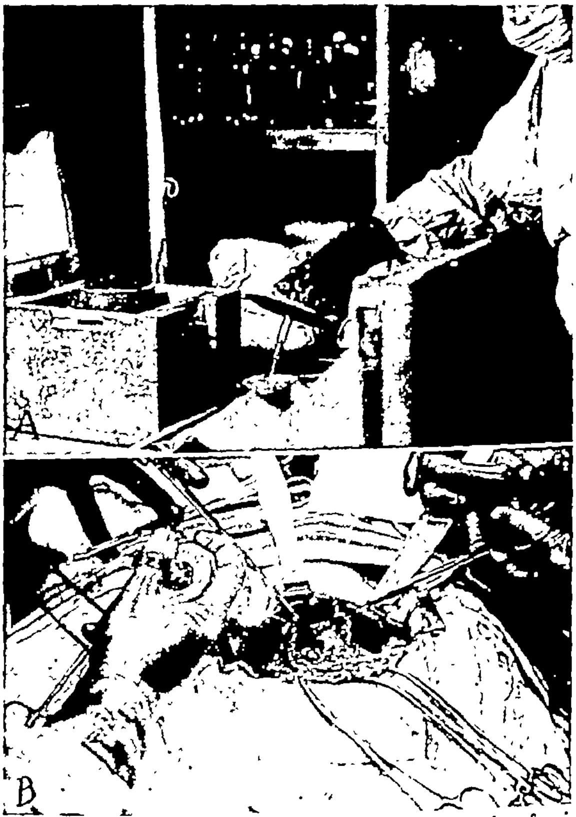

FIG. 1. *A*, filling of syringe with radio-active gold in preparation for injection. Guarded syringe is then handed to surgeon for injection, as illustrated in *B*. *B*, prostate exposed and material being injected. Note lead guarded syringe.

the circulation and probably is localized chiefly in liver and spleen. In no instance has there been clinical evidence of this, and in only 1 case has there been counts as high over the liver as over the prostate.

In order to get as adequate a distribution as possible, the combined retropubic-suprapubic approach is considered the best. It permits adequate exposure of the prostate, both intravesically and extravesically, the seminal vesicles and the regional lymph nodes. In the first few cases the puboprostatic ligaments were cut to allow greater mobilization of the prostate. It is now felt that this is unnecessary and by removing one of the fascial barriers actually is deleterious because it permits escape of some of the radio-active material. The bladder is opened and the material is infiltrated by multiple injections evenly distributed both transvesically and from the outside into the substance of the prostate, the seminal vesicle compartment and grossly involved lymph nodes. The bladder is then closed over a suprapubic catheter and a drain is used for the space of Retzius.

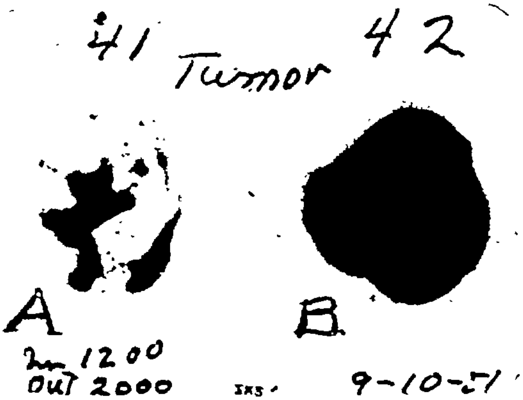

FIG. 2. Radio-autographs illustrating improvement in distribution of solution in mammary tumors in mice using hyaluronidase as diluent instead of saline. *A* shows autograph with saline. *B* shows autograph with hyaluronidase. Note improvement.

Originally the colloidal gold solution was diluted to a total volume of 15 to 30 cubic centimeters (depending on the volume of the growth) with saline. Because of the possibility of obtaining more uniform spread by the use of hyaluronidase, we have used a diluent composed of 100 cc of normal saline, 100 TU of hyaluronidase and 1 cc of 1:1000 epinephrin. Figure 2 shows the improvement in distribution of the solution in mammary tumors in mice with this diluent.

There is a good deal of evidence from our in vitro studies and from the pathologic studies of the material removed 3 weeks after instillation that the capsule of the prostate and the lymphatics and fascia about the seminal vesicles are very throughly infiltrated, but there is uneven infiltration in the substance of the prostate itself. This may be why the carcinomatous tissue in the periphery of the prostate seems to regress much more rapidly than that adjacent to the urethra. This would account for the fact that tumor may be found on the urethral surface of the prostate, while rectal findings show apparent complete disappearance of the tumor. This may also indicate that a combination of interstitial

TABLE 1.—*Treatment of carcinoma of the prostate with* Au^{198}

CASE			PREVIOUS HORMONAL TREATMENT	RECTAL ON ADMISSION	ESTIMATED VOLUME OF TUMOR CC	Au^{198} MC.	AT 3 WEEKS		AFTER 6 WEEKS		COMPLICATIONS		
No.	Name	Age					Rectal	Biopsy	Rectal	Biopsy	Rectal	Bladder	Other
1	T. H.	80	3½ months	4+	35	70	0	+	3 mos. 0	3 mos. 0	0	0	0
2	C. McG	68	2½ years	2+	22	64	0		6 wks. 0	6 wks. +	0	0	0
3	A. W.	65	0	4+	60	75	0	+			0	0	0
4	F. O.	73	0	2+	20	70	0	+			0	0	0
5	E. D.	59	1 month	2+	20	70	0		2 mos. 0		6 wks much ulcer	0	0
6	G. R.	69	0	4+	100	120	0-1+	+	6 wks. 0		0	0	transient leukopenia
7	H. R.	70	6 years	4+	90	100	0-1+	+	6 wks.		1 wk. slight	0	0
8	W. S.	60	9 months	3+	75	100	0-1+	+	6 wks. 0	8 wks. +	1 wk. slight	0	0
9	H. W.	60	1 year	4+	140	140	0-1+	+	6 wks. 0		0	0	0
10	W. D.	77	2½ years	4+	240	160	1+ hard	+	6 wks. 1+ hard		0	0	0
11	J. J.	68	0	2+	45	125	0-1+		0		2 wks. slight	0	0
12	J. S.	66	0	1+	50	94	0	+	0		3 wks. slight	0	0
13	G. R.	78	0	2+	80	67	0	0	0		0	0	0
14	W. D.	80	0	3+	100	67	0	+	0		1 wk. slight	0	0
15	F. G.	75	0	4+	70	140	1+ not stony hard	+			2 wks. slight	0	0
16	R. W.	62	0	2+	50	106	0				0	0	0
17	W. F.	78	0	2+	75	106	0				0	0	0
18	A. W.	66	3½ years	2+	50	106	0	+			2 days slight	0	0
19	T. S.	71	0	4+	85	93	0	+			0	0	0
20	R. H.	75	0	4+	150	93	1+ one nodule				0	0	0

radiation plus transurethral resection of the entire inner portion of the prostate 3 weeks later may be the treatment of choice in most cases.

Certain radiation hazards were anticipated and encountered. These concerned 1) measurement of the concentrated gold solution and its dilution; 2) protection of operating personnel during and after injection; 3) disposal of contaminated equipment, drapes, sponges and dressing; 4) isolation of the patient and disposal of his excreta. This has been the responsibility of the radiologists (H. D. K. and H. B. E.) working in conjunction with the radiation research laboratory. Measurement, dilution and transfer to the lead protected syringe used for injection is carried out in the operating room behind adequate lead shielding. Since the only protection after injection lies in speed and distance, every possible step in the operative procedure is completed before injection is started. Instruments with handles as long as practical are used from this point on. This phase, after injection through closure, seldom takes more than 10 minutes. Monitoring of the personnel with film badges and ionization chambers shows exposure well within permissible limits. With reasonable care there is no reason for contamination of operating room or operating drapes. They should, however, be carefully monitored after each session. Sponges used after injection is started should be placed in a separate container as they are frequently quite radio-active. These and contaminated syringes, instruments and any inadvertently soiled drapes are stored

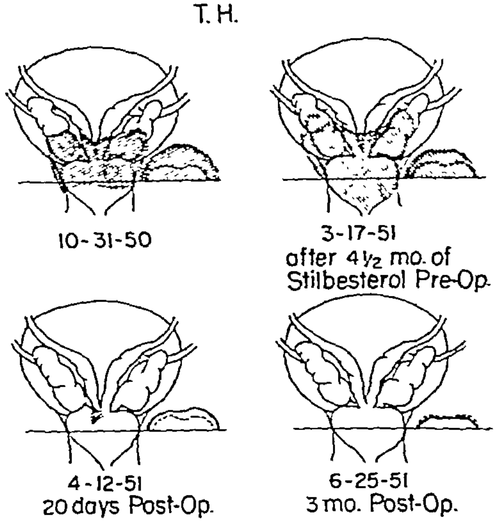

FIG. 3. Case 1. T. H., aged 80, admitted to University Hospitals on March 16, 1951 with known carcinoma of prostate of 5 months' duration. Patient had been on hormone therapy for 4½ months. Pathologic diagnosis, carcinoma of prostate. *A*, rectal findings October 31, 1950. *B*, rectal findings March 17, 1951. On March 23, 1951, 70 mc. of Au198 was infiltrated into tumor. Its volume was estimated at 35 cc. At time of operation, both seminal vesicles and both lateral lobes and periprostatic tissue on each side were involved. Lymph nodes could not be palpated. *C*, rectal findings April 12, 1951, twenty days postoperative. Transurethral biopsy on April 16, 1951 still showed carcinoma, but also showed extensive degenerative changes. Tissue biopsy removed transurethrally on June 26, 1951 showed no evidence of cancer. Rectal findings June 25, 1951 were essentially negative and are illustrated in *D*.

in a lead vault of the radiation research laboratory for a period of 3 weeks until their activity has died down to a safe level.

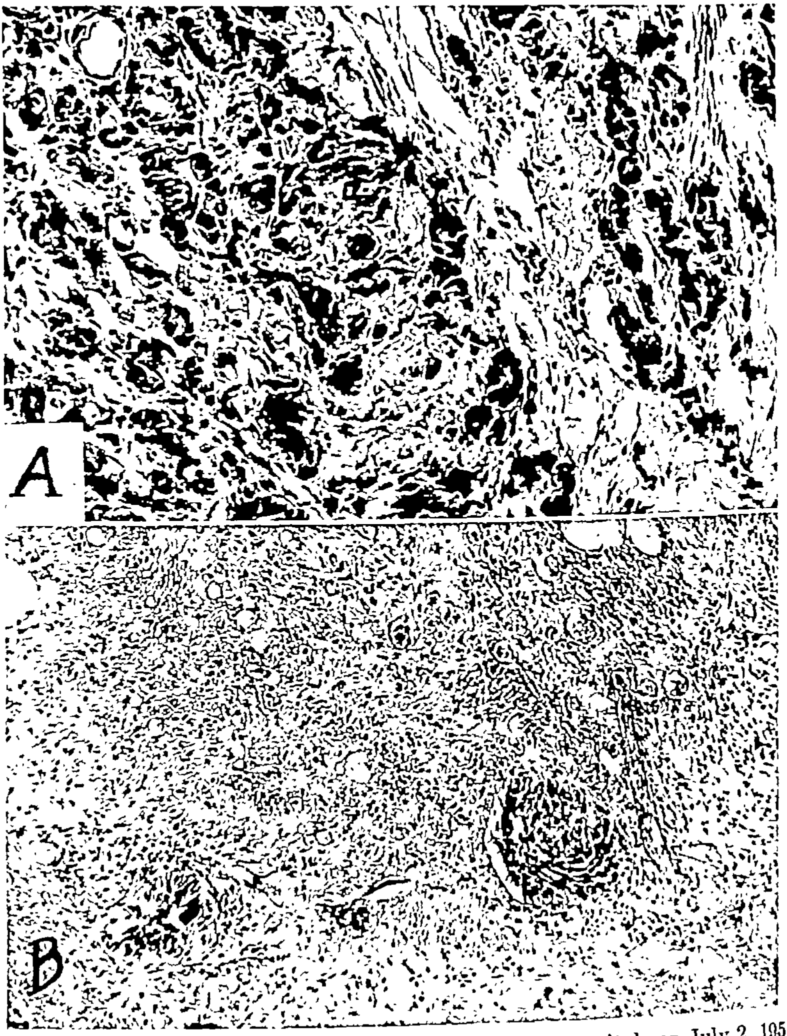

FIG. 4. Case 3. A. W., aged 65, admitted to University Hospitals on July 2, 1951 with tabes dorsalis and a hard, fixed prostate producing vesical neck obstruction. *A*, transurethral biopsy on July 5 showed carcinoma of prostate. *B*, microscopic appearance.

Patient was able to void satisfactorily, and rectal findings (fig. 5, *D*) showed no evidence of carcinoma. Checkup September 1951, showed patient to be well and rectal findings unchanged.

While a special room or ward for these patients is not necessary since even immediately after the operation a reading of less than 6 mr/h (maximum permissible exposure) is obtained outside a two-foot area surrounding the bed of the patient, it is well for visitors and nurses to stay away from this area except for necessary duties during the first 48 hours. The urine for the first 24 hours is usually quite radio-active (due to some seepage into the bladder) and is sent to the radiation laboratory for monitoring and disposal. It should not be flushed down the hospital plumbing. Dressings have proved no problem as their activity is negligible. All in all, radiation hazards are important, but need form no barrier to the use of this method if a radiologist, well trained in the use of radioactive isotopes, is a member of the team with the urologist.

RESULTS

The early results of treatment in this group of cases have been interesting and promising. In every case by the end of the third week there has been a tremendous change in the rectal findings. In each case there was rapid and prompt decrease in the size of the tumor. After the third week no evidence of hardness suggesting tumor could be found except in cases 9, 10 and 20. In all three of these patients, extensive decrease in size and hardness had occurred, however. (See table 1, and figures 3, 4 and 5).

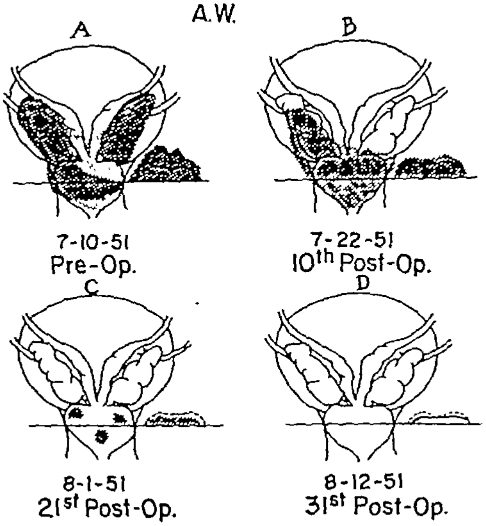

FIG. 5. *A*, rectal findings July 10, 1951 showing hard, fixed, large carcinoma of prostate. Retropubic exposure of prostate was done, and bladder and anterior portion of urethra opened to facilitate injection. Approximate volume of tumor tissue was 60 cc. Radio-active gold, 75 mc. total, was instilled into prostate and seminal vesicles. Prostatic urethra and bladder closed tightly, and bladder drained with indwelling urethral catheter. Postoperative course was uneventful. *B*, rectal findings July 22, 1951. *C*, rectal findings August 1, 1951. *D*, rectal findings August 15, 1951. Checkup biopsy on August 1, 1951 showed some areas of carcinoma which seemed to be in middle of tremendous areas of fibrosis and necrosis.

Microscopic findings are not as striking and promising as the rectal findings (table 1). In the first case, positive biopsy was noted at the end of the third week, but at the end of 3 months biopsy showed no tumor. Thus far, only three-week biopsies have been made in the remainder of the patients. In one no tumor was found (case 13). All the others showed tumor. There was a striking difference, however, between the histological appearance of the post-radiated tissue as compared with the pre-radiated tissue. There was extensive necrosis and fibrosis throughout. Here and there were large masses of tumor cells, many of which showed radiation changes. In other areas, however, masses of tumor cells

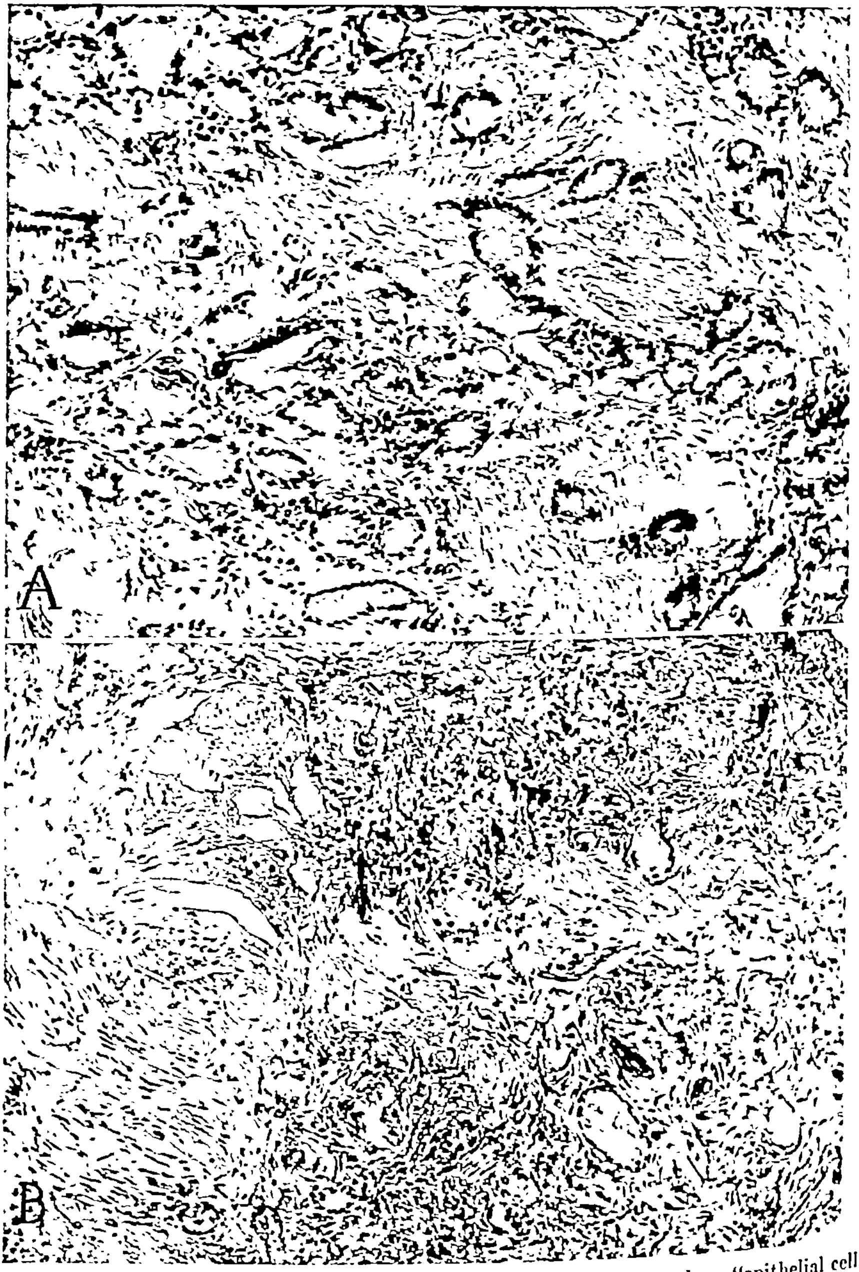

FIG. 6. Case 12. *A*, tissue removed prior to treatment. Sections show "epithelial cells arranged in strands, columns and small acini. Diagnosis: Adenocarcinoma of prostate." *B*, tissue removed from same area 3 weeks after interstitial radiation with Au198. Pathologic report: "Majority of tissue consists of partially hyalinized connective tissue with some necrosis and inflammation. One island of metaplastic glandular tissue is growing in solid buds which are invaded by connective tissue. In other areas there is the general tissue pattern of carcinoma, but tumor cells are disintegrated and in areas have disappeared. Diagnosis: Adenocarcinoma of prostate with radiation reaction."

without radiation changes were present. It will take many months of further study to determine the degree of neoplastic destruction (fig. 6).

Very few complications thus far, have occurred. The only serious one is that present in case 5. Bowel irritation developed within 3 weeks and rectal ulceration by the sixth week. The patient is quite comfortable on suppositories of opium and belladonna and a nonresidue diet. The rectal findings of carcinoma have disappeared and he is voiding well without any evidence of bladder irritation. No other ulcerations have occurred, thus far. In seven other cases of the 20 the patients had slight diarrhea lasting from 2 to 22 days which was readily controlled by the use of opium and belladonna suppositories. All others present no bowel irritations in spite of a feeling of edema between the rectal wall and prostate on rectal examination. Bladder irritation has not occurred. In 1 case mild leukopenia developed during the fourth week, but the patient recovered promptly. No typical gold reactions were noted. However, in 2 cases there was a slight reaction resembling shock which occurred immediately at the end of the operation which responded very readily to blood transfusions. The suprapubic wound healed rapidly and was closed completely by the end of 3 weeks. In every sense of the word, the procedure was strikingly free of complications or morbidity if one excludes case 5.

COMMENT

At the present time we think that the best technique for distribution is multiple injections and the use of epinephrin and hyaluronidase as a diluent. Undoubtedly better techniques will be developed in the future. Subsequent injections may be necessary to reach or control residual tumor. The gamma component may be favorable in that it destroys portions of the tumor which have not been directly infiltrated and, therefore, would not be affected by the beta radiation. It may very well be possible in the future to secure isotopes which emit pure beta radiation, have a satisfactory half life, can be injected locally and precipitate on injection so that no systemic spread occurs. Experimental work along these lines with compounds incorporating radio-active phosphorus is being carried out. Such compounds would make radiation hazard to the operator as well as the patient much less a factor, and make it possible to secure greater dosage. Combined instillations and multiple instillations through the perineum, transurethrally and retropubically may add to the effects produced thus far. Interstitial radiation treatment combined with hormonal treatment and surgical treatment may be even more effective. However, there is no question that even by the method used at the present time, tremendous destruction of the tumor, and in some cases apparently its complete eradication have occurred. It will take time, however, to know the complete effects of this type of treatment in these cases. Two facts stand out thus far: first, it is possible by this treatment to give intensive radiation to carcinoma of the prostate without producing quantitatively the complications which occurred in the past; and second, the problems of distribution within the tumor tissue are still incompletely solved.

SUMMARY

Preliminary experiences with interstitial radiation for carcinoma of the prostate using radio-active isotope Au198 in 20 cases have been described.

ADDENDA

Since the original paper was written in September 1951, an additional 36 cases have been treated. In general, results have paralleled those set forth in the foregoing discussion. However, the rectal complications have become more severe than the first follow-up survey indicated. As a result, intensive studies to obtain better distribution and avoid deposit of the radio-active material into the perirectal tissue have been conducted. An instrument (fig. 7) has been devised that will deliver a small volume under considerable pressure, which ensures better distribution with a smaller dose. A guard has been placed on the needle so that it cannot be inserted deep in the prostatic tissue or penetrate the prostatic capsule. The radio-active material is instilled in the tumor mass, both retropubically and transvesically, as illustrated (fig. 8). In addition to the foregoing precautions, the dose has been decreased. At the present time, a dose of one millicurie per gram of tissue is being used.

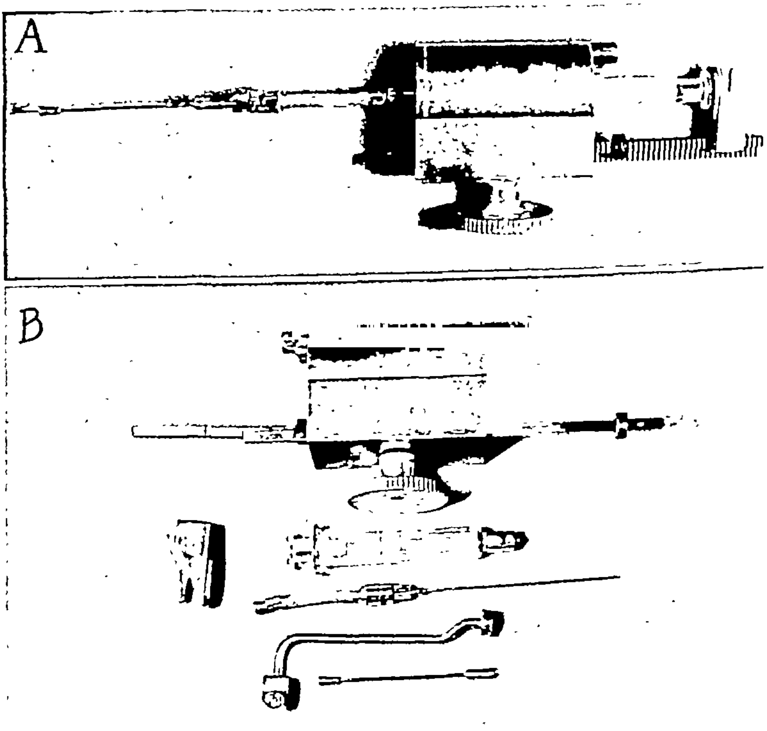

Fig. 7. Instrument devised for delivering small volume under considerable pressure. *A*, assembled. *B*, disassembled.

Four of the original 20 cases have expired, but none of the deaths were related to the carcinoma of the prostate or the therapy. The causes of death were: 1) testicular tumor with widespread metastasis, 2) uncontrollable diabetes mellitus, 3) possible myocardial infarction, and 4) pulmonary embolism. Of the remaining 16 cases, rectal complications have developed in 5 patients. All five have rectal scarring and stricture, while three have accompanying ulcerations. In 2 patients the rectal stricture is of a large caliber and asymptomatic. All of the ulcerations were examined through the sigmoidoscope and grossly appeared to be healing slowly.

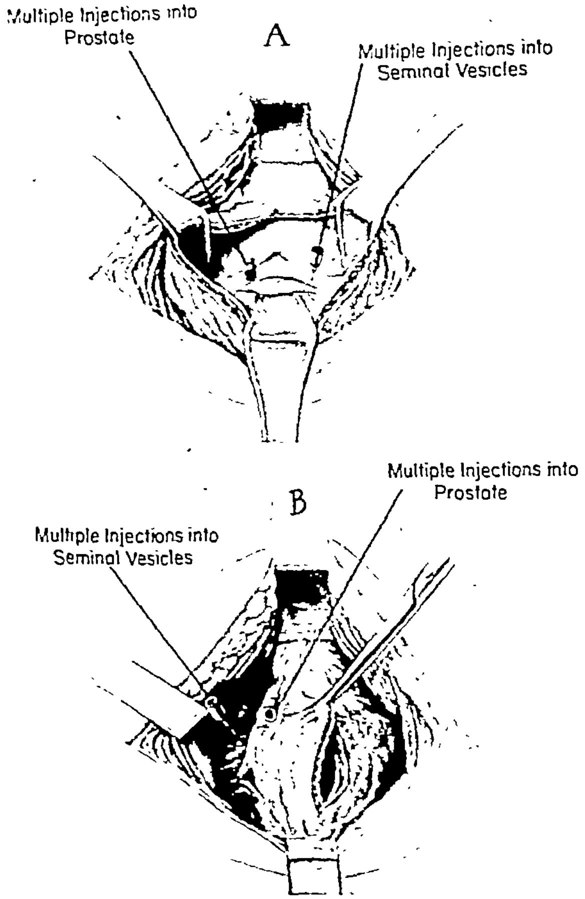
Multiple Injections into Prostate
A
Multiple Injections into Seminal Vesicles
Multiple Injections into Prostate
B
Multiple Injections into Seminal Vesicles

Fig. 8. *A*, transvesical instillation of radio-active gold into prostate and seminal vesicles. *B*, retropubic instillation of radio-active gold into prostate and seminal vesicles.

The greatest encouragement derived from the follow-up examinations was the fact that, even in the patients who had received what we considered an inadequate dose, control of the neoplasm had been achieved thus far. Rectal examinations on the 16 living cases (of the first group of 20 now 6 months or more postoperative) revealed that none of the prostates had the characteristic changes indicative of a neoplastic process. The first patient done over one year ago is living, well and asymptomatic. Rectal and other examinations still reveal no evidence of neoplasm.

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RADICAL RETROPUBIC PROSTATECTOMY FOR TUBERCULOSIS

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The need for a surgical procedure that permits of the complete extirpation of the tuberculous prostate and tuberculous seminal vesicles has long been felt by many urologists. Hugh Young, keenly appreciating the problems of genital tuberculosis, devised the radical perineal operation. In his own hands and in the hands of a few of his disciples this operation has been eminently satisfactory. Other urologists who attempted the procedure fared less well. Many have abandoned the operation. Its technical difficulties and its postoperative complications deterred many from performing it even when they believed that excisional surgery was indicated.

At Sea View Hospital perineal excision of the tuberculous prostate and seminal vesicles has been done from time to time by different operators. The results have not been encouraging, persistent urinary fistula being the most commonly encountered complication. Against this background of unfavorable operative and postoperative experience stands a growing awareness of the need for an excisional procedure applicable to a good many of our patients because serious complications of tuberculous prostatovesiculitis are not at all uncommon in our institutional practice. In an attempt to more clearly define the indications for radical excisional surgery of the tuberculous prostate we should like to recall some of its very real complications.

1) Caseation and rupture of prostatic abscess: Winer, in 1941, reported three such cases of spontaneous perforation into the rectum causing recto-urethral fistulas, acute ascending pyelonephritis and death. Rolnick has this to say on the subject of tuberculous abscess of the prostate: "There is, as in the case of the seminal vesicle, always more or less involvement of the periprostatic tissues, and sinuses which burrow into the perivesical and perirectal cellular tissue, can develop even as high as the space of Retzius".

2) Production of obstructive uropathy due to involvement of the lower ureter: The pelvic portion of the ureter where it courses close to the tip of the seminal vesicle may become involved in a marked inflammatory reaction around the vesicles. Our case 3 (SVH No. 1606) presents an example of such a process. Figure 1, *A* shows a mild degree of hydronephrosis in 1946. Subsequent films picture the progress of the disease. When the kidney and upper ureter were finally removed (September 1950) no evidence of tuberculosis could be found in either. We feel strongly that if this patient had been subjected to radical excision of the prostate and seminal vesicles in 1945 or 1946, his right kidney would not have been damaged by mechanical obstruction of the lower ureter.

3) Contracture of bladder neck with and without upper tract changes: We have seen numerous instances of varying degrees of this unfortunate end result of chronic prostatitis. Contracted bladder: We offer our case 4 (SVH No. 31257)

as an example, because this patient is clinically, radiographically, and bacteriologically free of upper tract tuberculosis which is usually suspected in the case of tuberculous cystitis.

4) Production of pain: In the 4 cases reported here severe intractable pain was the primary indication for surgery. The pain was referred to different areas of the abdomen and perineum, but in each case it could be reproduced by digital pressure on the prostate or a seminal vesicle. We do not imply that pain should be the only indication for excisional surgery. It is our impression that with the universal use of dihydrostreptomycin, pain frequency, and tenesmus have become less prominent symptoms irrespective of the tuberculous pathology present in prostate, seminal vesicle, or urinary bladder.

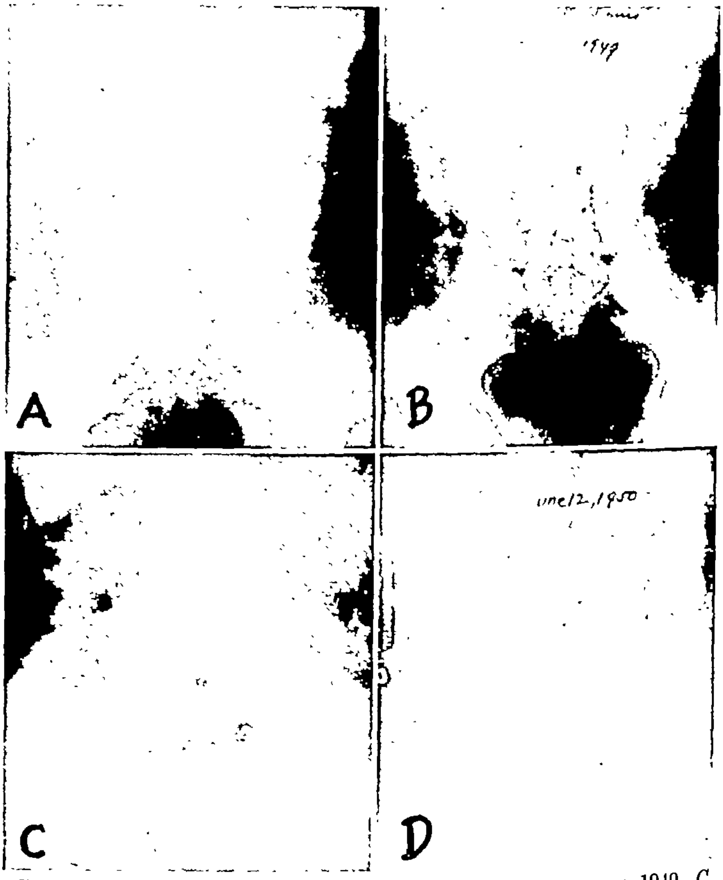

FIG. 1. Case 3. *A*, excretory urogram 1946. *B*, excretory urogram 1949. *C*, excretory urogram March 1950. *D*, retrograde pyelogram June 1950.

5) The tuberculous prostate a focus of infection: Again we should like to quote Rolnick: "in a few instances encapsulation ensues. . . . Wildbolz believes that such an apparent healing is deceptive and that virulent bacilli remain, so that recrudescence can occur at any time." Keeping this in mind, it is easy to realize the possible harm that may come from urethral instrumentation or pros-

tatic massage in the presence of tuberculosis. Although we ourselves have not seen cases of miliary tuberculosis directly traceable to such procedures, such cases are reliably reported by others.

Generally, we believe that minimal and moderately severe tuberculous involvement of the prostate and seminal vesicles should be treated medically unless symptoms or radiological evidence of one or more of the foregoing mentioned complications indicate excisional surgery. The presence of frank caseation or of discrete encapsulated nodular foci calls for surgical treatment. Of course, the patient's general condition and his pulmonary status must be taken into consideration, and close co-operation and co-ordination with the medical service are essential in every case.

DIAGNOSTIC ASPECTS

Considerable difficulty is encountered when one attempts to set up criteria for the diagnosis of tuberculous prostatovesiculitis. In typical cases the disease will be suspected when a patient with a known tuberculous lesion of the chest has urinary symptoms, low abdominal or perineal pain, or epididymitis. On rectal examination the prostate is apt to be irregularly enlarged with a nodular surface and the seminal vesicles are similarly involved. Such typical cases present no great diagnostic problem. We have not been impressed by the diagnostic value of seminal vesiculography. Cystoscopy and urethroscopy are performed routinely and are valuable aids diagnostically and prognostically, but no one typical pattern that might clinch the diagnosis has been evolved. Auerbach autopsied 105 cases of genital tuberculosis at Sea View Hospital and found that the size, shape, and consistency of the prostate gland were altered only when there was extensive tuberculous involvement of the prostate. In the cases reported here we relied heavily on pain symptoms, rectal findings, and the reproduction of pain by digital pressure on the diseased prostate or seminal vesicles.

OPERATIVE TECHNIQUE

We had some small but gratifying experience with the radical retropubic operation in cases of suspected carcinoma and purulent nonspecific prostatitis. In the summer of 1950, it occurred to us that we might put to use our working knowledge of the retropubic space and apply the procedure to cases of tuberculous prostatovesiculitis. With minor modifications the following technique was used. All patients received dihydrostreptomycin 0.5 gm. b.i.d. 1 week preoperatively and 6 weeks postoperatively. Spinal anesthesia was used in every case. The patient was placed in the supine position with a sandbag under his buttocks to hyperextend the pelvis. An 18F Robinson catheter was passed through the urethra; the bladder was irrigated clean and emptied. A 12 cm. long skin incision is made in the midline, beginning just below the superior margin of the symphysis pubis. The underlying rectus sheath is incised vertically and the recti muscles are retracted laterally. In our case 4 a Pfannenstiel type of incision was used and the recti muscles were transected just above their insertion in the symphysis pubis. (At the conclusion of the operation the recti had widely retracted and approximation was very difficult.) The prevesical space is demonstrated with the help of a moist sponge which wipes the peritoneal fold superiorly. A Balfour abdominal retractor is now inserted, and a malleable retractor is used instead of the third blade of the Balfour to depress the bladder. The anterior surface of the prostate is gently sponged free of adherent fat and a search is made for veins on the lateral and anterior aspects of the readily palpable gland. All veins are underrun with 0 catgut ligatures to prevent retrograde bleeding. The lateral fossae are now explored by gently freeing the lateral borders of the prostate with the index finger. The finger sweeps around the entire gland except for a small area posteriorly where its progress is arrested by recto-urethral fibers and the fascia of Denonvilliers. The periprostatic fossae are packed gently with 2 inch gauze. The puboprostatic ligaments are looked for and can usually be seen as ligamentous thickenings of the pelvic fascia running from the undersurface of the pubis to the region of the apex of the prostate. Between them run the dorsal veins of the penis. When the ligaments are well developed, they can be sectioned over a grooved director guide; this must be done on either side of the midline. There is often a brisk gush of venous blood which follows sectioning of the ligaments, and at first this caused us many anxious moments, for attempts to grasp the bleeding veins often fail. We have tried everything from electrofulguration to clamp and ligature and admit that this portion of the operation still is unsatisfactory. The best method of coping with the problem is to insert a roll of 1 inch vaginal packing under the symphysis and then have an assistant make firm pressure with a Deaver retractor over the packing. In the majority of cases the bleeding will have subsided in 10–15 minutes. We have started a transfusion of whole blood at this phase of the procedure in every case and we strongly recommend that 1500–2000 cc of blood be available for use.

The next step is to palpate the catheter in the membranous urethra and to gently lift that portion of the urethra with a Babcock clamp while depressing the underlying rectum with thumb and indexfinger. The apex of the gland is then sectioned with a long-handled scalpel. This is done by first incising the anterior wall of the urethra and placing a suture of chromic catgut No. 1 in the distal cut edge. The ends of the suture are left long and untied. The catheter is now withdrawn which makes it possible to complete the section of the urethra. The free apex of the gland is then caught with a long Kocher forceps and gently elevated. The finger is insinuated beneath the apex and the gland is bluntly freed from the underlying rectum. In spite of our efforts to establish a line of cleavage between the prostate and the fascia of Denonvilliers we were unable to do so in all those cases which, on pathological examination, were tuberculous.

The gland held in a tenaculum is delivered into the wound and turned over on itself. A transverse incision is made with scalpel over the base of the gland through the dense pelvic fascia covering the posterior surface of the prostate and seminal vesicles. This fascia is undermined and cut in an attempt to delineate the scarred and adherent seminal vesicles and ampullae of the ejaculatory ducts. Each duct is doubly ligated and cut between ligatures. Freeing the vesicles has been the most difficult portion of the operation. As a result of perivesicular chronic inflammation, these structures seem to be literally plastered to the undersurface of the bladder. In our cases 3 and 4, in order to facilitate dissection of the vesicles we incised the bladder neck anteriorly, located the ureteral orifices, and completed the incision along the entire circumference of the bladder neck, thereby separating the prostate from the bladder. The posterior commissure can then be grasped and elevated and the vesicles can then be bluntly freed from the bladder base. Prior to ligating the vascular pedicles of the vesicles we made it a point to identify the ureters. In two of our cases the rectovesical peritoneal pouch was accidentally entered. The rents were quickly noticed and repaired.

Bleeding points at the bladder neck are easily controlled by clamp and ligatures. The vesical neck and the stump of the membranous urethra were approximated over a Foley retention catheter (30 cc bag). The discrepancy in diameter was readily corrected by inserting a few interrupted sutures of chromic catgut in the anterior portion of the bladder neck. In our cases 1, 2, and 3 four interrupted sutures were placed in order to fasten the bladder to the membranous urethra. In our case 4 we relied entirely on catheter traction and splinting to effect the anastomosis. Two Penrose drains were placed in the retropubic space and brought out through the incision or through a nearby stab wound. The abdominal wall was closed in layers.

POSTOPERATIVE COURSE

Upon the patient's return to the ward the Foley catheter was connected to a closed irrigation and drainage system. In each case urinary drainage was observed within a few hours after the operation. The slightly sanguineous urine cleared by the morning of the second postoperative day. Irrigation of the bladder was unnecessary and was not used until suprapubic urinary leakage had completely subsided. This occurred between the seventh and eleventh (case 4) postoperative day. Continuous irrigation was then instituted for the remainder of the 12 day period; the outflow arm of the drainage system was raised above the level of the bladder to counteract contracture of the viscus. The Foley catheter was removed on the twelfth postoperative day.

All 4 patients complained bitterly of pain in the penile urethra and in the glans penis. This pain was the most distressing immediate postoperative complication. We believe that this pain is referred from the operative site. It is not relieved by removal of the catheter, but subsided in each case during the third postoperative week except in case 4 in which the patient continues to complain of pain in his glans penis.

The absence of abdominal pain and suprapubic distress was noteworthy. In this respect the reported cases fared as well as the patients who undergo retropubic enucleation operation. Paralytic ileus was not observed. Our case 2 had several bouts of vomiting; he had been subject to such episodes at frequent intervals for several years. Normal bowel function was spontaneously established within a few days in all 4 cases.

Most gratifying was the complete absence of shock in the immediate postoperative period. The operative time varied from 2–3 hours and blood loss was considerable. As we were dealing with debilitated patients we anticipated much greater postoperative depression. All our patients had been on bedrest prior to surgery and continued the same regimen in the postoperative period. We were on the lookout for postoperative venous thrombosis but found no clinical evidence of it. Tuberculous patients seem to be particularly immune to this complication.

OPERATIVE RESULTS

All 4 patients have been completely relieved of their most distressing symptom, pain. All wounds healed promptly; there are no postoperative sinuses or fistulas. There were no injuries to the rectum or to the ureters. Next to pain relief the functional result is of the utmost importance to the patient. Case 1, upon removal of the indwelling urethral catheter, had stress incontinence. Definite scar contracture at the site of the anastomosis was discovered on sounding. Following urethral dilation patient regained complete control of urination. He has had no urinary symptoms (D 4x, N 1x) since the seventh postoperative week. The result in case 2 has been less satisfactory. The urethral catheter was removed on the twelfth postoperative day. The patient had severe urgency and stress incontinence which persisted to the forty-second day when the urethra was dilated under anesthesia. Subsequent attempts at passing steel sounds met with an obstruction at the bladder neck requiring the use of filiforms. Partial incontinence recurred. Unfortunately, the patient's urethra is very sensitive to instrumentation. Urethral and bladder dilations at weekly intervals and stop-and-go exercises appear to improve the condition gradually. Most gratifying was the functional outcome of case 3. He has enjoyed complete urinary control since the twenty-fifth postoperative day, and he is free of urinary symptoms. The postoperative course of case 4 was complicated by poor catheter tolerance. He had severe purulent urethritis which failed to respond to aureomycin, penicillin, and sulfonamide. No peri-urethral abscesses can be palpated. A variety of microorganisms were identified in the discharge. The patient now has severe uncontrollable coughing bouts during which he is completely incontinent. His poor general condition precludes urethral instrumentation at this time.

CASE REPORTS

Case 1. J. H. aged 50, S.V.H. 30809, was admitted July 2, 1947. He had advanced bilateral upper lobe disease with multiple cavitation on both sides. He complained of no urinary symptoms at any time. Repeated urinalyses and 24 hour specimens for acid fast bacilli were negative.

The present illness commenced about May 1, 1950 with severe intermittent pain in the left lower quadrant and left inguinal region. The patient described the pain as "a deep drawing or pulling." The pain was not related to eating, bowel evacuation or micturition. He had no bowel symptoms except flatulence which had been a persistent complaint for 3 years. The pain radiated toward the left testicle, but there was no swelling of scrotal contents.

The pulse, temperature, respirations, and blood pressure were within normal range. No abdominal tenderness, rigidity, or masses were present. Some freely movable, small, hard lymph nodes were palpated in the inguinal region. On rectal examination the prostate was found to be 1 plus enlarged, smooth and regular, of uniform doughy consistency but markedly tender to palpation. The gland was not fixed. Seminal vesicles were palpable, smooth and round, extremely tender. Digital pressure on the left vesicle reproduced pain in the inguinal region.

Excretory urography and a series of gastro-intestinal films were negative. Because of the patient's poor condition cystoscopy was omitted. Smear of expressed prostatic secretion was reported negative for acid fast bacilli. The pain became progressively more severe and persistent, and large doses of opiates gave only temporary relief. Surgery was suggested as a last resort and readily accepted by the Medical Service and the patient.

On June 15, 1950 radical prostatovesiculectomy was done by the retropubic route. A considerable quantity of purulent material, thought to be the product of caseation, was accidentally spilled in the wound. The patient made an uneventful convalescence. His general condition is markedly improved. The pathological section prepared from the prostate showed only nonspecific inflammation but, on clinical grounds, we are certain that we were dealing with tuberculosis.

Case 2. J. B., aged 72, S.V.H. 34769, was admitted May 26, 1950. The patient had pulmonary tuberculosis and pleurisy with effusion. A laparotomy for tuberculous peritonitis had been done in June 1949. He also had arteriosclerotic heart disease and hypertension. The urogenital symptoms commenced June 19, 1950 with right epididymitis and hydrocele, urinary frequency (every 20 minutes) and painful urination. On rectal examination the left lobe of the prostate was nodular and stony hard. Urinalysis revealed many red blood cells and white blood cells. The nonprotein nitrogen was 45 mg. per cent. Excretory urography was unsatisfactory for diagnostic purposes. Urine from the bladder was positive for acid fast bacilli.

Cystoscopy: The bladder was small (200 cc capacity) and trabeculated. No ulcers or tubercles were seen. The ureteral orifices were negative. Intravesical enlargement, 2 plus, of a nodular left prostatic lobe was present, 1 plus on the right. Retrograde pyelography showed no gross deformities. Urine from the left kidney was negative for acid-fast bacilli on direct smear, positive by guinea pig inoculation. Right kidney positive (1 acid fast bacilli) on direct smear, negative on guinea pig inoculation. The serum acid phosphatase was not reported. A plain x-ray of the pelvis and lumbar spine showed no evidence of osseous metastases.

On July 6, 1950 radical prostatovesiculectomy was carried out by the retropubic route. Right epididymo-orchiectomy was done August 2, 1950. The patient's general condition appears improved. Pathological report: Tuberculosis of the prostate and seminal vesicles.

Case 3. O. N., aged 53, S.V.H. No. 1606, was admitted October 15, 1945. He had had known pulmonary tuberculosis since 1929. In August 1945 the patient had left epididymitis and epididymectomy. A postoperative sinus drained for about 6 months. Shortly after admission, the patient began to complain of day and night frequency. The diagnosis of tuberculous prostatovesiculitis was made in 1945, the prostate having been found enlarged and nodular. A 24 hour specimen of urine was positive for acid fast bacilli. Cystoscopy in 1948 showed chronic cystitis without tubercles or ulcers. Retrograde pyelography suggested a tuberculous process near the superior calyx of the left kidney, and a moderately dilated right pelvis. The right kidney urine was positive for acid-fast bacilli; no specimen was obtained from the left. The patient was given streptomycin from June 25–July 25, 1948. The effect on his symptoms was beneficial but transitory.

Early in 1950 the patient complained of severe burning on urination and frequency (nocturia 6 times). Urine from the bladder was positive. Excretory urography demonstrated severe degree of hydronephrosis on the right. Rectally, the prostate was considerably enlarged. Again, streptomycin was ordered; this time in conjunction with PAS. On completion of a 6 weeks' course of streptomycin, the prostate had shrunk and softened, but the seminal vesicles were still large and tender. Simultaneously with the reduction in size of the gland the patient experienced progressively severe pain in the perineum and in his suprapubic region. In June 1950, cystoscopic examination showed a remarkably silent bladder picture. In spite of unbearably severe symptoms there were no ulcers, tubercles, or infiltrations. Retrograde pyelography showed a far advanced hydronephrotic kidney on the right which eliminated indigo carmine poorly (fig. 1, *D*). The left kidney shows "early" tuberculosis. Bacteriologically, urine from both kidneys was positive for acid fast bacilli.

On July 13 radical retropubic prostatovesiculectomy was done, and on September 6, 1950 the right kidney and ureter were removed. Postoperative course entirely uneventful, all three incisions healing by primary intention. Patient is free of urinary symptoms. His general condition is markedly improved. Pathological report: Tuberculosis of prostate and seminal vesicles.

Case 4. S. T., aged 42, S.V.H. 31257, was admitted October 3, 1947. He had extensive bilateral pulmonary tuberculosis with several areas of cavitation. Ileocecal tuberculosis was suspected in 1949. In May 1950, the patient complained of severe burning on urination. The urine contained 15–20 white blood cells; twenty-four hour specimens were negative for acid fast bacilli. On rectal examination the prostate was of normal size, contour, and consistency; seminal vesicles palpable; the left was quite tender to digital pressure. Excretory urography showed normal upper tracts; the urinary bladder showed slight elevation of the base indicative of some degree of enlargement of the prostate. During the summer (1950) patient had bloody sputum and several episodes of massive pulmonary hemorrhage. He began to improve in August, but complained of severe pain in the left lower quadrant of his abdomen. The pain radiated toward his left kidney. He described it as a "crampy" pain, brought on by a full urinary bladder, and relieved by micturition. Rectal examination (August 25, 1950) again revealed enlarged seminal vesicles with marked tenderness on the left side. Digital pressure over the left seminal vesicle reproduced the pain in the left lower quadrant.

The bladder mucosa was dull and pale on cystoscopy. The wall appeared rigid and slightly trabeculated. The bladder capacity was 200 cc. Impression: Chronic cystitis. Retrograde pyelography showed no gross abnormalities. Urine from the bladder and both kidneys was negative for acid fast bacilli on direct smear; guinea pig inoculation was negative. Seminal vesiculography showed inadequate filling.

On October 23, 1950 the patient underwent radical prostatovesiculectomy by the retropubic route. Pathological report: Tuberculosis of prostate and seminal vesicles.

CONCLUSIONS

The radical retropubic operation is applicable to cases of tuberculosis of the prostate and seminal vesicles. The operation is well tolerated by poor risk patients, but provision for adequate blood replacement must be made. The chances of rectal injury and fistula formation are less than in the perineal operation. Partial incontinence, though temporary, has been a distressing complication in 3 out of 4 patients operated upon. We are considering the use of suprapubic catheter drainage in future cases in an attempt to prevent prolonged urethral irritation and its sequelae.

SUMMARY

The indications for excisional surgery of the tuberculous prostate are reviewed in the light of our experience at Sea View Hospital (a 1700 bed New York City institution for the tuberculous).

Four patients with suspected tuberculosis of the prostate underwent radical retropubic prostatectomy. The operative procedure is described and the postoperative results are evaluated.

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OBTURATOR CRUSH FOR OSTEITIS PUBIS

MAURICE MUSCHAT, GOTTLIEB S. LEVENTHAL AND JACOB KRAUSE

From the Urologic Department #1 and the Orthopedic Department #1, Albert Einstein Medical Center, Philadelphia, Pa.

This is a preliminary report of a new procedure for the relief of an excruciatingly painful condition of long standing, namely, the clonic spastic contractions of the adductor muscles of the thighs as seen in osteitis pubis. Sectioning of the obturator nerve brought about a dramatic immediate relief of pain in our patient who was bedridden for 3 months. He walked freely the day after the neurectomy.

While this operation has been done only on 1 case, we believe that it is our duty to report this immediately to enable others to give relief to their patients, instead of waiting for a large group which may take years.

Osteitis pubis occurs as a complication of operations upon the bladder, such as suprapubic or retropubic prostatectomy or resection of tumor; it has also been encountered following transurethral and perineal operations. The process is inflammatory and begins in the symphysis, gradually spreading downwards along the pubic rami to the ischial tuberosities. The symptoms begin several weeks after operation: pain in the groin on walking, gradually worsening, with the addition of excruciating spastic contractions of the adductor muscles of the inner thigh on one or both sides, completely incapacitating the patient and confining him to bed. Some have painful urination and defecation because of the spastic state of the levator ani and levator perinei, both attached to the inflamed periosteum. This condition lasts from 2 to 8 months or longer. X-ray evidence of bone destruction is not demonstrable before the sixth or eighth week. The pain gradually subsides, the bones ebonize and complete clinical cure ensues. No remedy up to date has been of any value.

We have had seven personal cases and have seen ten more in consultation. The pattern was the same, the sufferings alike and the therapy equally ineffectual.

The thought of attacking the obturator nerve has been with us for several years. We believed that if we could stop the painful contractions of the adductor muscles, even without altering the progress of the disease, the patient's suffering could be removed. We therefore began injecting the adductor muscles with novocaine, with immediate relief, but only lasting one to two hours. We also injected novocaine into the obturator foramen with immediate relief but also of only temporary value. We then requested our orthopedic department to actually attack the obturator nerve surgically. One would have to see the patient who was bedridden, with agonizing pain only a day before, take a painless and free walk after the neurectomy, to appreciate the dramatic effectiveness of this new procedure. The actual procedure is rather simple. A small incision is made over the inguinal region, the fascia cut, the muscles split, the peritoneum pushed inward, exposing the obturator foramen. The obturator nerve is easily identified and about 1 to 2 cm. removed. No drainage is needed.

The result of the neurectomy is a decrease of power of the adductor muscles. It actually does not incapacitate the patient. It is quite possible that crushing of the obturator nerve may be sufficient to tide the patient over the acute osteitis. In our case, however, because of his advanced age (70), it would have made very little difference, and we therefore performed a complete section.

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CARCINOMA OF THE SCROTUM: NEW APPROACH TO INGUINAL GLAND DISSECTION

M. W. COLEMAN, R. JOYCE AND R. S. GRAVES

Carcinoma of the scrotum was first described by Bessius in 1731.[1] Potts[2] in 1775 gave a classical description and associated the disease with occupation. Since then the disease has been one of importance, particularly in England. Between 1911 and 1935 there was 1,487 fatal cases on record with the Registrar General for England and Wales.[3] Numerous occupations were represented but generally it was and is confined to the laboring class. Particularly susceptible are those persons dealing with petroleum and its products. No cases were recorded in professional occupations.

In the United States the disease has been less common. Green[4] in 1910 recorded only 4 cases admitted to Massachusetts General Hospital in a 25 year period. The Brady Urological Institute recorded only 2 cases in 12,000 admissions.[5] Graves and Flo[6] reviewed the literature in 1939 and presented 14 cases. Dean presented 27 cases in 1938. In 1949, Higgins and Warden presented 8 cases observed over a twenty year period at The Cleveland Clinic.

The age at the time of onset is between 45 and 70 years. In Dean's series[7] there was a history of approximately 25 years exposure to tar or pitch in most instances. Workers in crude wool and soot are also prone to develop scrotal lesions. There is on record several cases of scrotal cancer in persons who had been receiving Fowler's treatment for psoriasis and in persons who received repeated x-radiation to the scrotum.

The tumor begins as a small warty growth often accompanied, or preceded by an itching sensation. Within a year, if nothing is done, the growth ulcerates, followed by pain and a more rapid spread. On the average, inguinal adenopathy develops twelve months after onset of the growth.

If the primary lesion is fungating, the adenopathy may be inflammatory and Dean recommends needle biopsy before radical gland excision.[7]

The malignancy spreads through the lymph channels. The work of Warren[8] reveals three factors which encourage this mode of dissemination: 1) The scrotum is richly supplied with lymphatics. 2) The location of the scrotum makes it subject to trauma and movement. 3) The absence of a sub-stratum in the scrotal wall prevents the usual tissue reaction with walling off of the lesion.

Read at annual meeting, North Central Section, American Urological Association, Toledo, Ohio, October 4, 1951.

[1] Bessius. Cited by Graves and Flo.[6]

[2] Potts: Cited by Henry.[3]

[3] Henry, S. A.: Study of fatal cases of cancer of scrotum from 1911 to 1935 in relation to occupation with special reference to chimney sweeping and cotton mule spinning. Am. J. Cancer, **31**: 28–57, 1937.

[4] Green: Cited by Higgins and Warden.[5]

[5] Higgins, C. C. and Warden, J. G.: Cancer of scrotum. J. Urol., **62**: 250–256, 1949.

[6] Graves, R. C. and Flo, S.: Scrotal cancer. J. Urol., **43**: 309–332, 1940.

[7] Dean, A. L.: Epithelioma of scrotum. J. Urol., **60**: 508–518, 1948.

[8] Warren: Cited by Graves and Flo.[6]

The prognosis for carcinoma of the scrotum is poor. Graves and Flo reported the average duration of life from onset of the disease to death to be 21 months. In Higgins and Warden's series of 7 patients, one was dead in 1 year and one in 6 years; two were unreported. The others were living 2 years or longer, but one with recurrence. In Dean's series of 7 cases without metastases when first seen, four were alive 5 or more years after treatment and of 16 patients with metastases when first seen, only two were alive 5 or more years later.

The only satisfactory treatment seems to be surgical excision. Morley's work[9] has shown that radiation is unreliable because the inguinal metastases are quite resistant and the thin scrotal wall offers a poor field for the radiation reaction necessary to destroy the malignant cells. Dean has shown that electrocoagulation, as well as all topical applications, is ineffective. Excision of the primary growth with the removal of a 1 cm. or more margin of skin should be done. Occasionally the testes have to be removed in order to re-approximate the scrotal skin. Likewise orchiectomy is indicated if the tumor has infiltrated the gubernaculum.

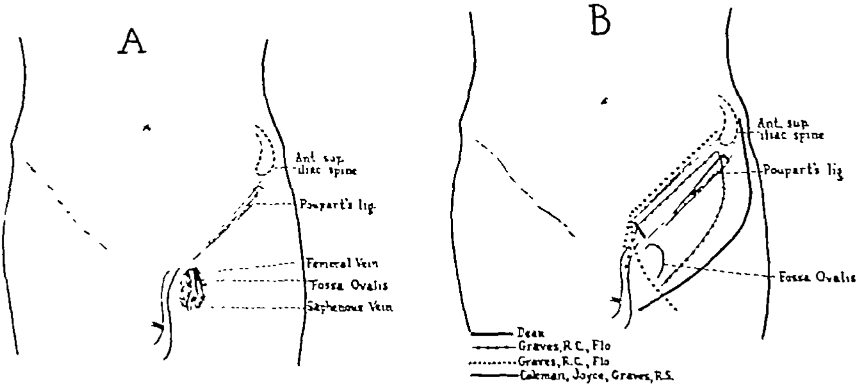

FIG. 1. *A*, semidiagrammatic sketch showing location of inguinal glands, as described by Morley. *B*, semidiagrammatic sketch showing location of incisions described by Dean, R. C. Graves and Flo, and also Coleman, Joyce and R. S. Graves.

Excision of the primary growth should be accompanied or soon followed by bilateral inguinal gland excision. The free communication between the lymph network on the two sides of the scrotum obliges the urologist to remove the contralateral glands as well as those on the side of the primary lesion. It seems wiser to do the two sides as separate procedures.

The incision to be used in removing the inguinal glands must be extensive enough to allow adequate exposure to the area of Poupart's ligament and to an area at the junction of the saphenous and femoral veins. Here Morley places the superficial inguinal glands about the intersection of two imaginary lines, one vertical and one horizontal. He locates the glands in four groups: supero-external and internal, and infero-external and internal (fig. 1, *A*). Occasionally efferent lymph trunks run from these glands to the deep femoral chain. Others may pierce the cribiform fascia and pass up the crural canal to end in the external iliac glands.

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[9] Morley: Cited by Graves and Flo.[6]

In addition, the incision must be so placed that the blood supply is not compromised and sloughing is minimized or prevented.

Dean has proposed an incision originating at the anterior-superior iliac spine and carried medially and down toward the pubis to end 2 cm. from the pubic tubercle. He then divides the inguinal ligament above the femoral canal. Graves and Flo reported extending the scrotal incision upward and parallel, laterally, to Poupart's ligament. At a point about 2 cm. from the anterior-superior iliac spine the incision is carried downward and inward to cross the lowest level of the femoral canal. The flap thus constructed is reflected medially. They have also suggested extending the scrotal incision up to communicate with an incision identical to that described by Dean. A third line of incision is then carried down and outward from that junction to pass across the base of the femoral triangle. A large lateral flap is thus developed.

We propose an incision which originates on the anteromedial surface of the thigh at a point about three inches from the inguinoscrotal junction. The incision is carried lateralward and slightly upward to the anterolateral surface of the thigh where it turns up to end about two centimeters above and lateral to the anterior-superior iliac spine. Such an incision does not dissect the skin immediately over the involved glands and results in a flap reflected upward and medially, affording adequate exposure of the lymphatic glands and ducts, the ligaments, the fascia and the vascular pattern of the inguinal area. The wide base permits a good blood supply usually resulting in primary healing. See figure 1, *B*.

The following is a case of carcinoma of the scrotum which demonstrates one application of the incision we have just described for inguinal gland dissection. The same incision might be used in carcinoma of the penis or vulva, or in any other situation requiring dissection in the inguinal area.

G. H., a well developed and nourished married white man, aged 63, presented himself on May 1, 1951 complaining of a "sore on the scrotum." He stated that approximately 12 months prior to that he had first noticed an area of hardness on the left side of the scrotum about the size of a dime. The patient was not concerned with this lesion until 4 months before visiting us when it "cracked open" and seemed to drain slightly. The patient applied various patented ointments without benefit. Shortly after beginning to drain the lesion began to increase in size and remained painless except for the discomfort of rubbing against his clothes. The patient had no other complaints and the past history was negative. The social history did not reveal exposure to oils or resins and did not give any indication of trauma to the area involved.

The physical examination revealed only the changes on the scrotum and in the groins. On the left side near the inguinal junction was a raised, circular lesion, 3 centimeters in diameter. The edges were rolled and the center was necrotic (fig. 2, *A*). On palpation, the lesion was evidently confined to the skin and muscle of the scrotal wall. There was marked enlargement and induration of the left inguinal glands. The right inguinal glands were similarly changed but to a lesser degree. The routine laboratory studies were negative.

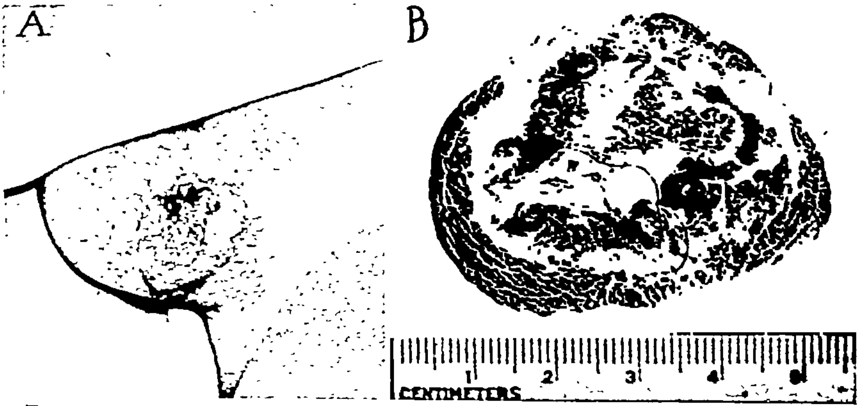

FIG. 2. *A*, photograph of lesion prior to excision. *B*, gross lesion after excision

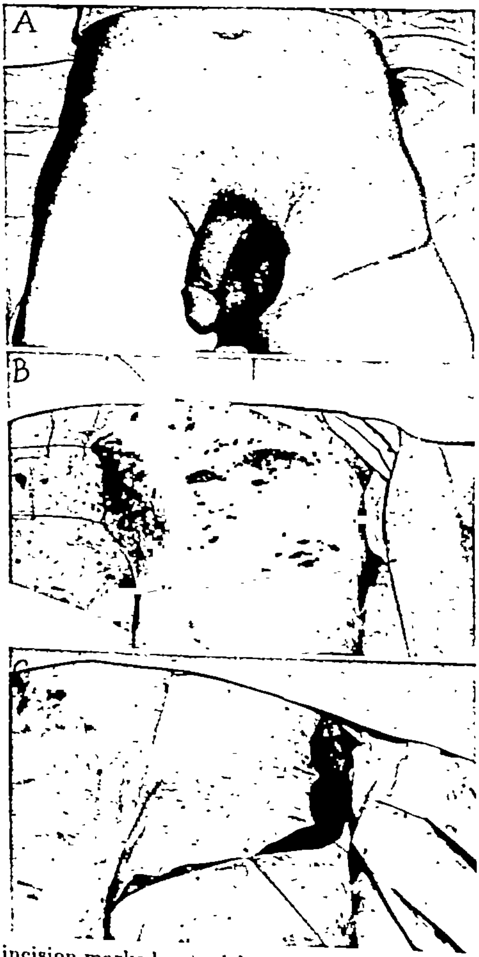

FIG. 3. *A*, line of incision marked out with gentian violet. *B*, flap reflected medially. *C*, flap replaced ready to approximate edges of original skin incision.

On May 8, 1951 the lesion was excised (fig. 2, *B*). The pathologist reported it to be an infiltrating, horny, squamous cell carcinoma with ulceration and superficial pyogenic infection.

On May 23, 1951 an attempt was made to excise the left inguinal glands. As described previously, an incision was made originating 3 inches below the inguinoscrotal junction on the medial aspect of the thigh. The incision was extended obliquely laterally to the anterolateral aspect of the thigh then upward to 1 inch superior and lateral to the anterosuperior iliac spine (fig. 3, *A*). The flap thus formed was reflected by using silk traction sutures. Care was taken not to traumatize the edge with clamping instruments (fig. 3, *B*). All bleeders were ligated with triple (O) plain catgut sutures. The saphenous vein was found to be nearly completely compressed by indurated tissue which on frozen section proved to be squamous cell carcinoma. The vein was doubly clamped, severed and ligated. The entire block of malignant tissue was then removed by sharp and blunt dissection. There was extensive invasion of the fossa ovalis and the femoral and external iliac glands. Removal of these deeper structures could not be accomplished without sacrificing the femoral and external iliac vessels and was not attempted. The skin flap was then sutured to the underlying deep fascia with triple (O) plain catgut stutures and the edges were approximated with four (0) black silk sutures. (fig. 3, *C*). A small Penrose drain was placed beneath the skin flap through a stab incision 1 inch below the thigh incision. Such a drain is necessary to prevent accumulation of serum beneath the flap. A pressure dressing was then applied.

The sutures were removed on the eighth postoperative day and the patient was discharged on the twelfth postoperative day, at which time the incision was healed and the skin flap was viable except for an area on the midthigh, 3 inches long, and ¾ inches wide. This area subsequently healed by granulation. A small amount of serum continued to be expressed from beneath the flap through the drain site until the twenty second postoperative day. Generally the patient's course has been steadily downhill. At the time of this writing he is bedfast and will no doubt soon succumb to his disease.

In conclusion we have briefly reviewed the historical background of carcinoma of the scrotum and presented the clinical features and accepted means of treatment. We have proposed a surgical approach to inguinal gland dissection which we believe is heretofore undescribed. This approach has the advantage of wide exposure followed by primary healing in the majority of instances. A case of carcinoma of the scrotum has been presented in which application of this approach has been demonstrated.

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THE POTENTIALITY OF THE PERITONEUM AS A DIALYZING MEMBRANE

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The value of the peritoneum has not been fully appraised as a substitute for temporary loss of renal function in reversible renal injuries. In the past quarter century, according to Odel, a few more than 100 cases have been reported. An analysis of these cases indicates that the procedure has been singularly unsuccessful. This was undoubtedly due to the employment of unsuitable perfusion solutions and to errors in technique. Few patients' lives have been saved as a result of peritoneal lavage; to the contrary, many have succumbed to complications as a result of the procedure.

Any artificial dialysis is unnecessary in a properly managed patient in the early phase of anuria, i.e., the first week to ten days. If anuria persists beyond this time, some form of dialysis such as peritoneal lavage, artificial kidney, and intestinal lavage may be effective in prolonging the life of the patient and increasing the chances of recovery. Peritoneal lavage in the past has been instituted early in renal failure, when such a procedure was unnecessary, and its use usually evoked changes which did not prolong life but, instead, may have increased the mortality. Furthermore, perfusion solutions used for peritoneal lavage have resulted in profound changes in the body fluids and electrolytes, such as depletion of chlorides, dehydration, edema, hemoconcentration, shock, and other imbalances leading to fatal consequences.

It is not the purpose of this report to review fully the known physiology of the peritoneum as a semipermeable membrane. Information pertaining to its physiology must be gained from past experiments and clinical experiences. The peritoneum is not an inert membrane, although it obeys in many respects the known laws of osmosis and diffusion. It is lined by living cells through which various substances have different diffusion rates (glucose much slower than sodium and chlorides). Indeed, even particulate matter such as bacteria and erythrocytes are absorbed through the peritoneum. Experimental data indicate activity of the cells themselves, as fluid and substances in general tend to be absorbed into the blood stream against an osmotic gradient. The irritative action of any perfusate solution may increase the rate of diffusion due to capillary dilatation, and a warm solution may have a similar effect.

The peritoneum should theoretically be an efficient membrane for dialysis because the surface area is approximately 22,000 square centimeters. The total surface of the filtering membrane of the glomeruli is only 15,000 square centimeters, but there is a much greater volume of blood on the opposite surface of the glomerular tuft when compared to the peritoneum. In many respects, the peritoneum behaves as a simple dialyzing membrane such as the cellophane

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employed in an artificial kidney. Crystalloids diffuse across semipermeable membranes until there is an equal concentration on both sides. Substances of larger molecules, such as proteins and colloids, do not normally permeate such membranes. It is evident that the exchanges that take place across membranes are determined by the concentration of diffusable substances in solution on the two sides together with the osmotic pressure that they exert in the respective solutions. For example, peritoneal perfusion solutions containing sodium chloride in greater concentration than that of the blood plasma soon cause marked changes within the fluid compartments of the body. Sodium chloride shifts rapidly through the peritoneum into the plasma, increasing the concentration of these electrolytes in the latter, producing hypernatremia and hyperchloremia. This is accompanied by a shift of water from the cells into the extracellular compartments, resulting in edema. Such shifts could easily cause circulatory embarrassment, pulmonary edema, and cardiac failure. For another example, the injection of a perfusate solution of 5 percent glucose results in electrolytes diffusing from the plasma into the glucose solution, producing dehydration and a shift of water from the plasma and extracellular spaces into the body cells. Such changes in body electrolyte and fluid patterns are inimical to recovery in anuric patients.

It is evident that a perfusion solution must be so constituted in order that no undesirable exchanges of fluid or electrolytes will occur across the peritoneum to disturb the electrolyte pattern of the plasma. If the perfusate solution employed fulfills this criterion and has as its composition an electrolyte pattern and osmotic pressure similar to that of the blood plasma, a marked diffusion from the blood into the perfusate of nitrogenous and many other undesirable waste products should result.

It is our purpose here simply to report recently accumulated data which indicate the potentialities of the peritoneum for dialysis. In the past, only negligible data on the chemical aspects of peritoneal extraction have been recorded. Odel et al. have reported on extraction of urea in 4 cases of peritoneal perfusion for acute renal failure (table 1).

In table 1 it can be seen that they extracted from 0.52 to a maximum of 1.54 gm. of urea per liter of perfusate, with an average of 1.05 gm. of urea per liter.

The patient from whom the following data were acquired was a young man, age 25, in anuria for eleven days. Although he was properly managed, it was evident at that time that there was hyperkaliemia and that toxic products were beginning to accumulate within the body. As a result, we instituted daily peritoneal lavage on the eleventh day for a period of nine days. A solution was used in this case as indicated in table 2.

Concentration of the electrolytes in this perfusion solution closely approximated that of those in the plasma of the patient. Glucose was added in order to increase the osmotic pressure and prevent loss of water from the perfusate into the body. It is well known that the osmotic pressure of the plasma in anuria or renal failure is elevated above that of the normal. By means of freezing point depression, it was determined that the solution had an osmotic pressure of 350 mOs, which is well above the 311 mOs of the normal plasma. The above solution, while ideal for this particular patient, might not be suitable for every case. The osmotic pressure of the plasma as well as the electrolyte patterns should, therefore, be determined for each individual case, following which a proper solution can be easily constructed.

From a mechanical standpoint, perfusion in the past has been performed in two ways. The first is the continuous flow type. An intake tube is inserted into the peritoneal cavity through one of the lower quadrants of the abdomen, usually on the left, with a counter tube on the right for egress of the perfusate. The second type is instillation of the perfusate into the peritoneal cavity through a closed system, where it is allowed to remain for one to two hours. The continuous method is theoretically more ideal because it allows a moving solution of constant composition to be in contact with the peritoneum at all times. In the employment of the intermittent procedure, fluid and electrolyte exchanges begin to take place between the plasma and the instilled perfusate, resulting in a gradual change in osmotic pressure of the latter. This disadvantage is more than offset by the fact that in continuous perfusion the fluid tends to channel among the intestines and mesentery from the points of ingress to that of egress, with the result that only a small surface area may be in contact with the perfusate. In the instillation technique, the patient can be gradually turned from side to side so that a large surface area of the peritoneum is likely to be contacted by the solution, thus increasing the efficiency. It is our practice to insert a polyethylene tube under strict aseptic conditions through the left lower quadrant with a trocar. This is attached to a closed sterile perfusion apparatus. Antibiotics such as aureomycin and penicillin may be added to the perfusion solution. As a result of such precautions, peritonitis need no longer be a major complication. Employ-

TABLE 1. *Data on extraction of urea (Mayo Clinic)*

CASE	TOTAL CC PERFUSATE	TOTAL GMS. UREA	GMS. UREA/LITER PERFUSATE
#1	92,750	143.2	1.54
#2	64,258	68.9	1.07
#3	117,715	60.9	0.52
#4	95,240	101.0	1.06

Average (4 cases) gms. Urea/Liter/Perfusate: 1.05

TABLE 2. *Perfusate solution*

GM./LITER		mEq/LITER	
NaCl	5.77	Na	134
$NaHCO_3$	3.0	Cl	105
$CaCl_2$	0.25	HCO_3	35
$MgCl_2$	0.1	Ca	4.5
		Mg	2.5
Glucose	30.0		
mOs			350

ing this technique, we irrigated the peritoneum in this patient with 5,000 cc of the foregoing solution for 2 days and then 10,000 cc a day for 7 days. The polyethylene tube remained in place for 13 days, during which time perfusion was performed on 9 days. One thousand cubic centimeters of solution were instilled into the peritoneum, where it remained for an hour and a half and then was aspirated. It is of interest that no fluid exchange occurred in this patient, because we recovered all of the 80,000 cc of instilled perfusate.

During the nine day period of perfusion, a total of 419.2 grams of urea was extracted (table 3).

TABLE 3. *Urea extracted*

38.26 gm.
56.84
42.
57.8
44.5
57.2
64.9
25.2
32.5
419.2 gm. (9 days)

Average 9 days 46.5 gm./day; 5.2 gm./liter perfusate.

TABLE 4. *Total protein*

32.7 gm.
42.
35.
103.1
28.5
42.4
57.5
31.3
372.5 gm. (8 days)

(Probable 9 days 416.6 gm.)

This is an average of 46.5 gm. per day or 5.2 gm. per liter of perfusate, or approximately five times the amount of urea per liter of perfusate reported in the experiences of Odel and his associates using continuous lavage (table 1). This large amount of urea is not as much as can be removed with the artificial kidney, which under optimum conditions of blood flow has been reported to extract 10 to 12 gm. per hour. The amount daily removed here required approximately fifteen hours of perfusion, making the dialysis of urea with the artificial kidney approximately 400 per cent more efficient on an equal time basis. Removal by artificial kidney is, however, a complicated procedure and would necessitate a number of so-called "runs" to remove an amount of urea equal to the 419 gm. extracted in this case. Peritoneal lavage is a far more simple procedure and certainly more applicable to a large number of patients with anuria or acute renal failure. Technical personnel and facilities for the use of artificial kidney are available only in medical centers. It should be stressed that urea is nontoxic, and its removal is not of prime importance in uremia. It may serve, however, as an index of the extraction of more toxic nitrogenous products and unknown organic acids.

TABLE 5. *Potassium extracted*

1.74 gm.
2.42
1.68
2.78
2.11
2.46
2.85
1.45
1.24
18.73 gm.

(480 mEq total, 9 days).

TABLE 6. *Phosphorus extracted*

1.12 gm.
1.37
1.0
1.10
0.89
1.06
1.06
7.60 gm. 7 (days)

(Probable 9 days 9.7 gm.)

TABLE 7

URIC ACID EXTRACTED	CREATININE EXTRACTED	CREATINE EXTRACTED
1.21 gm.	2.19 gm.	0.61 gm.
1.57	2.95	0.62
1.09	2.06	1.23
3.87 gm. 3 days	2.97	1.17
(Probable 11.61 gm.)	2.09	0.55
(in 9 days)	2.67	1.33
	3.22	1.04
	18.17 gm. 7 days	6.55 gm. 7 days
	(Probable 23.35 gm. 9 days)	(Probable 8.41 gm. 9 days)

The amount of total protein removed was 372.5 gm. in 8 days (table 4). Calculated for a period of 9 days, 416.6 gm. were probably extracted. It may result from chemical irritation of the peritoneum, since theoretically the large protein molecule does not diffuse across the membrane. The nature of the protein extracted in peritoneal lavage is obscure. It is unknown whether such large amount of protein represents toxic products. In our patient it did not result in hypoproteinemia, because the plasma proteins remained between 14 and 16 mEq per liter.

The potassium cation was purposely omitted from our perfusate solution. As in a previous publication, we have pointed out that potassium is potentially toxic, especially in anuria where the main route of excretion is blocked. Table 5 shows that in the 9 days of perfusion a total of 18.73 grams, or 480 mEq, of potassium were extracted—approximately 32 times the total quantity of potassium in the plasma of a normal individual. The plasma potassium, which was 8.5 mEq per liter at the beginning of lavage, dropped promptly to 5 mEq per liter.

From table 6 it can be seen that a total of 7.6 gm. of phosphorus was removed in 7 days. It was not calculated on 2 days, but on the basis of the average removal for 7 days, it is evident that in 9 days approximately 9.7 gm. were extracted. A number of potentially toxic substances may be associated with phosphorus. It is well known that in uremia phosphates tend to be elevated, resulting in a reciprocal lowering of plasma calcium and tetany.

Table 7 shows the amount of uric acid, creatinine, and creatine removed during the extraction period. When calculated on a 9-day basis, it is evident that we removed more than 11 gm. uric acid, 23 gm. creatinine, and 8 gm. creatine. In such a patient with a marked caloric deficit, creatinine, not normally present in the urine, indicates tissue, and especially muscle, breakdown.

At the end of the perfusion period, which was 25 days after the onset of anuria, the patient showed no clinical evidence of uremia, as a satisfactory fluid and electrolyte balance was maintained. At the insistence of the family, the kidneys were explored at that time and were found to be completely necrotic. Under these circumstances, the peritoneal lavage tube was removed, and the patient was allowed to die. At autopsy, the kidneys were found to be completely destroyed. There was little evidence of peritoneal reaction as a result of the employment of the above aseptic perfusion technique. We are convinced that lavage could have been continued in this case, with the further extraction of large amounts of undesirable substances, including many unknown organic acids and toxic compounds.

SUMMARY

These data have been reported to indicate the potentiality of the peritoneum as a dialyzing membrane. We believe that the usefulness of the peritoneum has been overlooked. Peritoneal lavage is a relatively simple procedure and most applicable to a large number of patients. It should again be emphasized that it is not practical in all cases of acute renal failure, for example, following postoperative intra-abdominal operations, ileus, or marked adhesions. The artificial kidney, intestinal and peritoneal lavage all have their indications and value in specific instances of acute renal failure. All should be instituted only when indicated. To date, they have been used either incorrectly or at a period when they were unnecessary, so that one cannot appraise their value or conclude that any of these procedures has saved many lives. As a result of peritoneal lavage

there have probably been far more fatalities than there have been lives saved. With appreciation of the proper mechanical features of the procedure and the use of a correct solution, it is evident from the data reported here that the peritoneum is a highly efficient membrane for the diffusion and removal of undesirable products from the plasma and body fluids during temporary renal failure.

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USHING'S SYNDROME DUE TO ADRENAL CORTICAL ADENOMA. A SURGICAL CURE

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Surgical cure of a patient with Cushing's syndrome due to an adrenal cortical denoma is sufficiently rare to warrant the reporting of such a case.

CASE REPORT

(MSH No. 602788) D. F., a 26 year old single white woman, was admitted o the Mount Sinai Hospital in December 1947, complaining of severe back ain. She had been well until 2 years prior to admission when she was hospitalized elsewhere because of a similar attack of back pain which diminished on ed rest. During the past few years she had had attacks of sudden pain in the ibs accompanied by a peculiar snapping sound. The pain would decrease after everal weeks, only to recur. Six weeks before admission while bending, she eard a loud snapping noise in her back following which severe pain developed n the lumbar region. She remained in bed and subsequently sought hospitalization because of persistence of the pain.

Although her menses had been normal and regular until the age of 26, she had had amenorrhea during the 2 years prior to admission. During the past few years she had noted slight hirsutism and puffiness of the face and a 20 pound gain in weight. There had been no change in her voice.

The physical examination revealed obesity localized to the trunk of the body, and a moon-like facies (fig. 1). The hair distribution was normal except for a mild hypertrichosis of the upper lip, cheeks, and temple. The teeth were in very poor condition. Many areas of point tenderness were present over her ribs. The blood pressure was 150/95 mm. of mercury. Purple striae were present over the lateral aspects of her breasts, abdomen, and thighs. No abdominal masses were palpable. The clitoris was not enlarged and the pelvic examination was negative. The extremities were thin, and ecchymotic areas were present on her thighs and legs. A marked kypho-scoliosis was present and tenderness was noted upon palpation of the lower thoracic and lumbar spine. The neurological examination was negative.

The laboratory examination revealed the blood count to be normal except for a relative neutrophil polynucleosis. The urine showed no abnormalities. The erythrocyte sedimentation rate was 70 mm./hour. The blood urea nitrogen, the serum chloride, carbon dioxide content, cholesterol, and total protein examinations were all normal. The serum calcium and inorganic phosphorus levels were normal, but the alkaline phosphatase was elevated to 39 King-Armstrong units. The serum sodium was 156 mEq/liter. The glucose tolerance curve was diabetic in character. The urinary excretion of the neutral 17-ketosteroids was 4.2 mg./24 hours (within the normal range). The basal metabolic rate was minus 34 per cent. A marked generalized osteoporosis was demonstrated by means of x-ray examination. The sella turcica was roentgenologically normal. Multiple (fifty-three) fractures of the ribs and sternum were present as well as compression fractures of all the lumbar and some of the thoracic vertebrae (fig. 2). Excretory urograms were normal. No abnormality was noted after bilateral perirenal insufflation in conjunction with excretory urography even with tomographic technique.

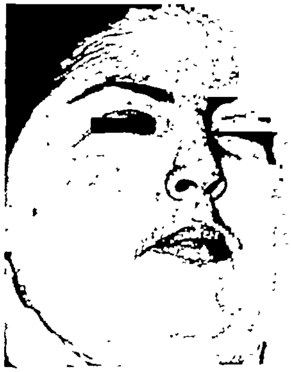

FIG. 1. Appearance before operation. Note moon-like facies and hirsutism

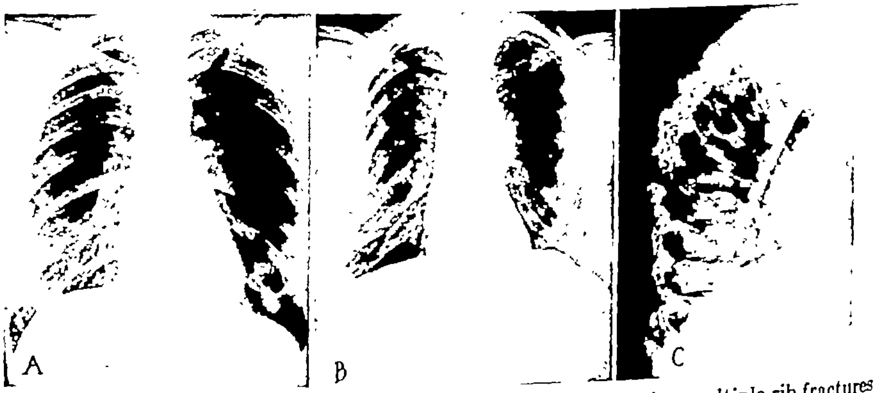

FIG. 2. *A*, x-ray of thorax 2 years before illness. *B*, demonstrating multiple rib fractures and deformities. *C*, showing multiple compression fractures and osteoporosis.

In view of the absence of a demonstrable adrenal tumor by x-ray, a diagnosis of diffuse bilateral adrenal cortical hyperplasia was made.

Androgenic therapy was instituted in an effort to increase the deposition of protein matrix in the skeletal system and thus aid in the recalcification of the bones. X-rays taken 1 month later showed no improvement, but rather an increase in osteoporosis and further collapse of the lumbar vertebrae was demonstrated. Because of the rapid progression of the disease, more definitive treatment became imperative. With a view to possible unilateral adrenalectomy, exploration was decided upon.

In March 1948, a left lumbar adrenal exploration was performed (G. D. O.), the left side being chosen arbitrarily. After careful exploration of the left suprarenal area, a small thin rim of adrenal tissue estimated to be less than 1 gm. in weight was found high under the left crux of the diaphragm. It was realized that the atrophy of the left adrenal reflected the probable presence of a functional contralateral cortical tumor. Therefore, the atrophic adrenal gland was left undisturbed. The postoperative course was uneventful except for the status of the operative wound. The wound failed to heal by primary intention and gaped following removal of the sutures. Eventual healing took place over a period of four months.

Three months after the first operation, in June 1948, following preoperative preparation with whole and lipo-adrenal cortical extract, a right lumbar adrenal exploration (G. D. O.) was performed. In the suprarenal area a smooth encapsulated, yellowish-brown tumor about 3 cm. in diameter and weighing 9.6 gm. was seen. The tumor was removed leaving behind a very small fragment of atrophic adrenal tissue. The pathology report was "fragment of adrenal gland with cortical adenoma of the adrenal (fig. 3). Microscopically, with routine hematoxylin and eosin stain, the tumor is seen to consist of fairly uniform cells, arranged in irregular clusters and networks separated by capillaries. The nuclei are small and moderately dark staining while the cytoplasm shows a variable lipoid content. No cell atypism, nuclear hyperchromatism, or mitoses are seen. There is one focus of degeneration with cholesterol deposition present" (fig. 4).

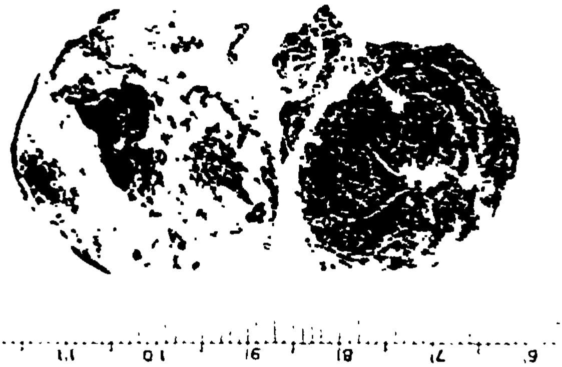

FIG. 3. Adenoma of adrenal cortex

The patient tolerated the procedure well and her clinical condition remained good until 12 hours postoperatively when a precipitous fall in blood pressure developed and the clinical picture of shock. She was treated vigorously with large doses of whole and lipo-adrenal cortical extract, continuous intravenous infusion of glucose in saline, the parenteral administration of adrenalin in oil, and a continuous intravenous drip of neosynephrine. Despite this vigorous treatment she remained in profound shock for 36 hours with a systolic pressure of 70–80 mm. mercury. The blood pressure then rose to 110/70 mm. of mercury and she appeared somewhat improved clinically. The course during the next few weeks was stormy and marked by sudden episodes of shock which gradually responded to the administration of adrenal cortical extract and parenteral fluids. Eventually it was possible to reduce the dosage of supplementary adrenal cortical extract and to discontinue it. Subsequently, it was readministered for short periods on several occasions when loss of appetite, weakness, and hypotension suggested some degree of adrenal insufficiency.

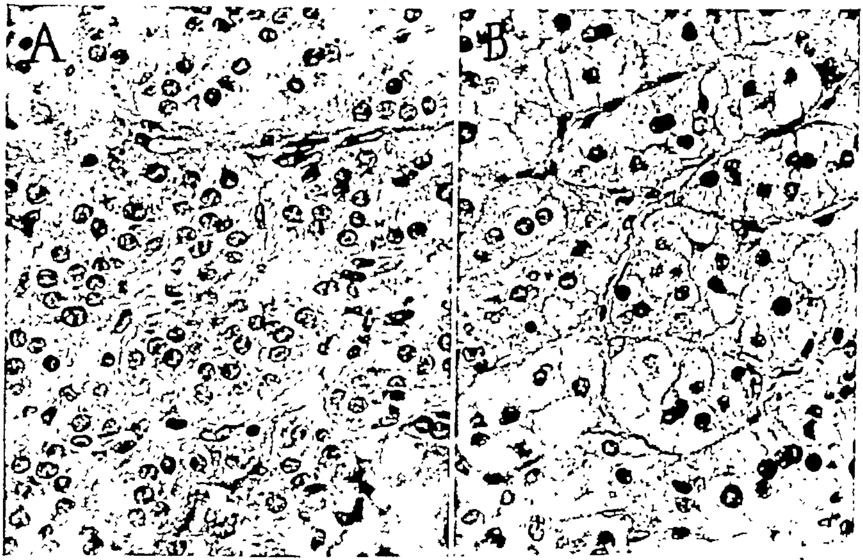

FIG. 4. *A*, low power photomicrograph. *B*, high power photomicrograph

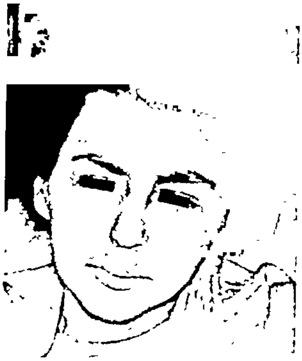

FIG. 5. Postoperative appearance

During the immediate pre- and postoperative period, the patient received the following specific hormonal therapy: Four hours before operation, 5 cc of lipo-adrenal cortical extract intramuscularly and 10 cc of whole adrenal extract subcutaneously were given. Immediately prior to operation she received 5 cc of lipo-adrenal extract intramuscularly, 20 cc of whole extract intravenously and 20 cc subcutaneously. During the course of the operation she was given 1 cc of lipo-adrenal extract intramuscularly and 5 cc of whole extract intravenously twice. Postoperatively the dosage was 3 cc of the lipo-adrenal extract intramuscularly and 5 cc whole extract subcutaneously at first every hour and later every three hours. During the period of postoperative shock she also received 0.5 cc of adrenalin in oil (1:500) subcutaneously every ½ hour and neosynephrine 8 mg. per hour by continuous intravenous drip.

In addition, her postoperative course was complicated by failure of the wound to heal, and final healing occurred after many months by secondary intention. A phlebothrombosis of the inferior vena cava developed and also a bizarre cerebral picture characterized by a toxic psychosis and neurological signs suggestive of cerebral arterial thrombosis. The compression fractures of the spine and a postoperative contracture of the left leg presented major orthopedic problems in her rehabilitation. She was finally discharged from the hospital in December 1948, approximately 6 months after removal of the adrenal adenoma. At that time a partial contracture of the left leg was her sole residual disability.

In October 1949, 16 months postoperatively, she was re-admitted to the hospital for study. Her menses which had returned in March 1949, were now regular. The change in her appearance was striking. The face had assumed its normal contours and the peri-orbital puffiness and facial hirsutism had disappeared (fig. 5). The obesity of the trunk was markedly diminished and the purple striae were now white scars. The blood pressure was normal. The serum sodium was normal and the glucose tolerance curve which had been diabetic in character was now flat. The basal metabolic rate, previously minus 34 per cent, was plus 2 per cent. Three years after operation the patient was in excellent health and asymptomatic.

DISCUSSION

In 1932 Cushing[1] described 12 instances of a syndrome which he ascribed to pituitary basophilism since he found the disorder to be frequently associated with a basophilic adenoma of the pituitary gland. Although examples of the syndrome had been described prior to his report, the eponym of Cushing's disease was subsequently applied to it. Since this paper, however, instances of Cushing's syndrome have been noted not only in conjunction with pituitary basophilic tumors but also in association with other types of pituitary tumor and with either diffuse hyperplasia or tumors of the adrenal cortex. Less commonly it has been associated with tumors of the thymus or "arrhenoblastomas" of the ovary or has even been found in the absence of any overt endocrine pathology.[2, 3] As a consequence many authors have denied Cushing's concept of primary pituitary basophilism especially since it has become increasingly apparent that whatever the primary cause of the disorder, the clinical manifestations are the result of adrenal cortical hyperfunction. Included among the evidence marshalled against Cushing's thesis was the fact that although basophilic adenomas were encountered in 3.1 per cent of the 127 pituitaries examined by Brauchli,[4] in 3.1 per cent of the 260 pituitaries reported by Susman,[5] and in 7.2 per cent of a series of 1000 patients studied by Costello,[6] in none of these patients were there any evidences of Cushing's syndrome. However, such observations did not necessarily eliminate a causal relationship between that type of tumor and Cushing's disease since eosinophilic adenomas occur in patients without acromegaly or gigantism and no one denies such an etiological relationship. Furthermore, hormonally inert adrenal cortical tumors are common. Some light was shed on the pituitary adrenal inter-relationship in Cushing's syndrome by the observations of Oppenheimer and his associates.[7,8] In 24 instances in which a basophile adenoma of the pituitary was found in the absence of Cushing's disease, the adrenals were all normal. On the other hand, in 18 of 24 instances of Cushing's syndrome pituitary basophilic adenomas were found. In one other patient an increase in the number of basophiles was present in the pituitary gland. In 16 of these 24 patients there was an associated adrenal cortical hyperplasia and in only 4 were the adrenals normal. To these observers, the findings suggested that although pituitary basophilic tumors need not result in Cushing's syndrome, when there was such an association, the clinical manifestations were mediated via the adrenal cortex. Further clinical evidence of the importance of the role of the adrenal cortex in producing the picture of Cushing's syndrome was afforded by the finding of adrenal cortical tumors in the absence of gross pituitary changes. In addition, thymic tumors encountered in conjunction with this disorder are invariably associated with adrenal cortical hyperplasia[9] and so-called "arrhenoblastomas" producing this syndrome appear to be tumors of aberrant adrenal cortical tissue. This concept of the importance of the adrenal cortex in the genesis of the Cushing syndrome was also accepted by Thompson and Eisenhardt[2] who collected 98 instances of Cushing's syndrome with autopsy findings. However, they did not report on the correlation between pituitary and adrenal cortical disease. In 60 cases, pituitary adenomas were found, only 49 of which were basophilic. In 22 cases an adrenal cortical tumor was encountered of which 16 were malignant and 6 were benign. In one a thymic tumor was found, in another an "arrhenoblastoma" and in 12 no demonstrable tumor of any gland was observed.

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Several important physiological findings explain the pathological observations encountered in Cushing's syndrome. It had been reported by Smith[10] that hypophysectomy results in adrenal cortical atrophy. On the other hand, later observations revealed that the administration of pituitary extracts or preferably the purified adrenocorticotropic fraction produced adrenal cortical hypertrophy.[11,12] The recent clinical demonstrations that Cushing's syndrome can be

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produced by the prolonged administration of 17-hydroxy-11-dehydrocorticosterone (compound E, cortisone) or of adrenocorticotropin, would tend to resolve the dispute as to the role of the pituitary and the adrenal cortex in the genesis of the naturally occurring disease picture. It seems likely therefore that the primary site of the clinical disorder may be either the pituitary or the adrenal cortex. It remains to be demonstrated, however, that in those instances of Cushing's syndrome attributed to pituitary basophilism there is actually an increased secretion of adrenocorticotropin.

Recent observations also explain the pathological findings of Crooke.[13] This investigator described a peculiar hyalinization of the basophile cells of the non-adenomatous areas of the pituitary gland in patients with Cushing's syndrome. Of the 12 patients studied, 6 had basophilic adenomas, 3 had thymic tumors and 3 had adrenal cortical disease. These observations have since been confirmed,[2] but their true significance has been widely debated. It had been suggested that these findings represented evidences of pituitary hyperactivity or contrariwise that they were merely the manifestations of pituitary hypofunction secondary to adrenal cortical secretion. In a recent autopsy study on patients who had received cortisone therapeutically, these hyaline alterations were found in the pituitary gland.[14] It thus appears that the hyaline alterations represent changes incident to a high level of circulating adrenal cortical hormone.

It must be emphasized that not all instances of adrenal cortical hyperfunctions are associated with the clinical features of Cushing's syndrome. In general, the adrenal cortex produces at least 3 types of hormone, a salt retaining hormone resembling in action that of desoxycorticosterone; glycogenic corticosteroids for which compound F is the prototype; and a group of sexogens including androgens, estrogens and progesterone. The evidence available would suggest that the salt retaining hormones are formed in the zona glomerulosa, the glycogenic corticosteroids in the zona fasciculata, and the sexogens possibly in the zona reticularis. Overproduction of any of these groups of steroids results in a characteristic syndrome. The androgenital syndrome be it of a virilizing or feminizing nature is a purely sexual syndrome resulting presumably from an overproduction of one or more of the sexogens. This syndrome is discussed in detail in a paper on the "Virilizing Syndrome" by Soffer, Gabrilove and their associates.[15] The syndrome encountered in association with the overproduction of the salt retaining hormone is not as yet clearly delineated but recently such a case has been observed in our hospital and is to be reported elsewhere.

The overproduction of the glycogenic corticoids is associated with the syndrome under discussion. Clinically the most striking manifestations of Cushing's syndrome consist of the development of a moon shaped facies, a buffalo-like obesity, plethora, hypertension, amenorrhea in females, purple abdominal striae, a diabetic glucose tolerance curve, osteoporosis, purpura and ecchymoses. In addition, there is often noted weakness, asthenia, mental changes, polyuria and polydipsia. The disorder is far more common in females than in males in a ratio of 4 or 5 to 1. It is quite uncommon in the post menopausal age group and occurs far more frequently postpuberally than prepuberally. It is now known that many of these manifestations result from the nitrogen wastage encountered in this disorder and can be produced in the normal subject by the administration of compound E or adrenocorticotropin. Further details as to the physiological basis for the clinical manifestations of the disease are discussed by Soffer and Gabrilove.[16]

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[13] Crooke, A. C.: J. Path. and Bact., **41**: 339, 1935.

[14] Laqueur, G. L.: Science, **112**: 429, 1950.

[15] Soffer, L. J., Gabrilove, J. L., Jailer, J. W. and Jacobs, M. D.: Recent Progress in Hormone Research, vol. 5, p. 407, 1950.

The diagnosis can be established by the demonstration of an increased urinary excretion of the glycogenic corticosteroids (the 11 oxycorticoids)[17, 18, 19] and by the demonstration of a positive salt tolerance test.[20, 21] On occasion, a hypochloremic alkalosis is encountered which presumably reflects depletion of the potassium stores of the body. The blood picture is usually that of a polymorphonuclear leukocytosis, lymphocytopenia and eosinopenia.

Proper therapy is dependent on the underlying pathological lesion. Since the manifestations of the syndrome reflect adrenal cortical hyperfunction, it is necessary to decide whether the disorder results from an adrenal cortical tumor or diffuse adrenal cortical hyperplasia. If a tumor is present, especially if it be benign, surgical cure may be hoped for. If the adrenal lesion is hyperplasia, radiation of the pituitary with a total dosage of 4000 r is indicated. Not infrequently this may result in amelioration of the clinical picture. If, however, no improvement is noted following this mode of therapy, unilateral adrenalectomy should be performed although the likelihood of resultant cure is not great.

The diagnosis of the presence of an adrenal tumor may be facilitated by means of two procedures. One of these is perirenal insufflation in conjunction with laminography. A negative result however does not exclude the presence of a tumor. A second aid is afforded by means of the measurement of the 24 hour urinary excretion of the neutral 17-ketosteroids. In general, one may say that *in the presence of diffuse hyperplasia the urinary excretion of these compounds* is normal or only slightly elevated. If the underlying lesion is a benign tumor the values encountered are usually normal whereas the urinary excretion of these steroids, especially the beta fraction, is markedly elevated with carcinoma. However, these findings are not invariable.[22-27]

Not infrequently it is advisable to explore the adrenals in order to exclude the presence of a tumor. In a series of 21 instances of adrenocortical tumor associated with obesity in children, Marks and his associates found the left adrenal to be involved in 75 per cent of the cases.[28] It would therefore seem advisable, especially in view of its anatomical accessibility, to explore this side first if the site of a suspected tumor is not known.

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[16] Soffer, L. J. with the assistance of Gabrilove, J. L.: Diseases of the Endocrine Glands. Philadelphia: Lea and Febiger, 1951.

[17] Venning, E. and Browne, J. S. L.: J. Clin. Endocrinol., 7: 79, 1947.

[18] Daughaday, W. H., Jaffe, H. and Williams, R. H.: J. Clin. Endocrinol., 8: 244, 1948.

[19] Talbot, N. B., Albright, F., Saltzman, A. H., Zygmuntowicz, A. and Wixom, R.: J. Clin. Endocrinol., 7: 331, 1947.

[20] Soffer, L. J., Gabrilove, J. L. and Jacobs, M. D.: J. Clin. Invest., 28: 1091, 1949.

[21] Soffer, L. J., Lesnick, G., Sorkin, S. Z., Sobotka, H. and Jacobs, M. D.: J. Clin. Invest., 23: 51, 1944.

[22] Engstrom, W. W.: Yale J. Biol. and Med., 21: 21, 1948.

[23] Walters, W. W. and Sprague, R. G.: Ann. Surg., 129: 677, 1949.

[24] Talbot, N. B., Butler, A. M. and MacLachlan, E. A.: N. Eng. J. Med., 223: 369, 1940.

[25] Wilhelm, S. F. and Gross, S. W.: Am. J. Med. Sci., 207: 196, 1944.

[26] Forbes, A. P., Carroll, E. L. and Wheeler, M. L. J.: Clin. Endocrinol., 9: 680, 1949.

[27] Luft, R.: Acta Med. Scandin. Supp. 149, 1944.

Benign tumors causing Cushing's syndrome are less common than malignant lesions. According to Wilkins,[29, 30] adrenal hyperplasia as a cause of Cushing's syndrome is uncommon in children under the age of ten. However in the series of 27 instances of Cushing's syndrome in children under the age of 16 collected by Farber and his associates,[31] they observed a pituitary basophilic adenoma in 8, an adrenal cortical tumor in 4, adrenal cortical hypertrophy in 4 and a thymic tumor in one. In the adult, however, the incidence of adrenal cortical hyperplasia in association with this syndrome exceeds that of tumor. The high incidence of malignancy when the syndrome is due to an adrenal cortical tumor is shown by the figures reported by Thompson and Eisenhardt who noted that 16 of 20 instances of adrenal cortical tumors associated with Cushing's syndrome were malignant. In Wilkins' series of 70 instances of adrenal cortical tumor in children producing the adrenogenital and/or Cushing's syndrome, malignancy was proven in at least 30. Of the 24 instances of adrenal cortical tumors associated with obesity in children collected by Marks and his associates, only 4 were stated to be benign adenomas. Furthermore of the 12 instances of adrenal cortical tumor collected by Engstrom[22] in his compilation of the urinary excretion of the neutral 17-ketosteroids in Cushing's syndrome, only one was an adenoma. Only one out of 8 cases of Cushing's syndrome due to tumor reported by the Mayo Clinic was benign.[23, 32, 33] On the other hand, in a series studied by Cahill and Melicow[34] a benign lesion was encountered in 4 out of 5 instances of adrenal cortical tumor in association with Cushing's syndrome. Weinberg[35] in a series of 34 cases of this disorder due to adrenal tumor found 80 per cent to be malignant. In general, therefore, it may be concluded that the incidence of a benign cortical tumor is less common than that of a malignant tumor in those instances of adrenal cortical neoplasm producing Cushing's syndrome.

The surgical removal of an adrenal cortical tumor associated with Cushing's syndrome is fraught with great danger. In 1933, Cecil[36] although not giving details, remarked that the mortality rate was high and that this was usually due to atrophy or absence of the contralateral gland. Indeed he stated that in 30 per cent of the cases, the "suprarenal opposite to the one occupied by the tumor was absent or inadequate to support life." Since his report, the importance of contralateral adrenocortical atrophy or absence in patients with Cushing's syndrome due to adrenal cortical tumor has been repeatedly emphasized.

[28] Marks, T. M., Thomas, J. M. and Warkany, J.: Am. J. Dis. Child., 60: 923, 1940.
[29] Wilkins, L.: J. Clin. Endocrinol., 8: 111, 1949.
[30] Wilkins, L.: Adv. in Ped., 3: 159, 1948.
[31] Farber, J. E., Gustina, F. J. and Postoloff. A. V.: Am. J. Dis. Child., 65: 593, 1943.
[32] Walters, W. and Kepler, E. J. Ann. Surg., 107: 881, 1938.
[33] Walters, W., Wilder, R. M. and Kepler, E. J.: Ann. Surg., 100: 670, 1934.
[34] Cahill, G. F. and Melicow, M. M.: J. Urol., 64: 1, 1950.
[35] Weinberg, J.: N. Y. State J. Med., 41: 884, 1941.
[36] Cecil, H. L.: J. A. M. A., 100: 463, 1933.

In 1941, Weinberg collected 34 instances of adrenal cortical neoplasms reported in the preceding 14 years. In 21, the contralateral adrenal was atrophied, in 2 it was absent and in 10 it was normal. More recently Spence and Thompson[37] have reviewed the literature in this respect. It is also now apparent, as emphasized by Cahill[38] that it is the metabolic or Cushing syndrome, rather than the adrenogenital syndrome that is associated with these contralateral changes. Indeed Cahill[37] has found that removal of a tumor associated with the adrenogenital syndrome is relatively safe, whereas removal of a tumor associated with Cushing's syndrome is frequently fatal. The physiological reason for contralateral atrophy in Cushing's syndrome due to adrenal cortical tumor is now evident since the demonstration that the administration of adrenal cortical extract or preferably compound E induces cortical atrophy.[39]

It is thus obvious why the mortality rate following surgery for adrenal cortical tumor in Cushing's syndrome has been so high in the past. Thompson and Eisenhardt in a collected series reported that all 18 patients subjected to surgical removal of the tumor had died. The statistics published by the Mayo Clinic however, have been considerably better. However, in all reported cases except one from the latter group the underlying lesion was malignant. In some of these instances but undoubtedly not all, some functioning metastases were left in situ. It is therefore understandable why the operative mortality reported in instances of adrenal carcinoma associated with Cushing's syndrome is better than that in benign tumor.

It is difficult to find reports of a successful surgical removal of benign adrenal cortical tumors associated with Cushing's syndrome. One case each has been reported by Wilhelm and Gross,[25] Walters and Sprague,[23] and Cahill and Melicow.[34]

Patients with a benign lesion successfully operated on are cured. The prognosis in those with malignant lesions who have been successfully operated on is not apparently hopeless. Of 70 instances of adrenal cortical tumors causing both the adrenogenital and/or Cushing's syndrome collected by Wilkins, 14 were said to be cured. However he did not separate those with Cushing's syndrome alone. In general, the prognosis in carcinoma is poor, death usually occurring within a year. Nonetheless, in a case of adrenal cortical carcinoma associated with Cushing's syndrome studied at our hospital and reported by Goldstein[40] the child is well 4 years postoperatively. A similar instance was reported from the Mayo Clinic. In 18 cases of adrenal cortical tumor associated with obesity not subjected to surgery reported by Marks and his associates, death occurred in a period of 4 to 48 months.

It is apparent that a successful surgical outcome in Cushing's syndrome caused by adrenal tumor is dependent on the type of underlying lesion as well as on the pre- and postoperative management. Hitherto specific replacement therapy has been attempted with the use of whole adrenal cortical extract and more recently

[37] Spence, H. M. and Thompson, F. G. Jr.: N. Eng. J. Med., **236**: 13, 1947.
[38] Cahill, G. F.: Surgery, **16**: 233, 1944.
[39] Ingle, D. J. and Kendall, E. C.: Science, **86**: 245, 1937.
[40] Goldstein, H. M.: Arch. Dis. Child., **78**: 260, 1949.

lipo-adrenal extract in addition to the parenteral administration of fluid and salt. The use of desoxycorticosterone also has been advocated by some observers. The case reported is an instance of successful surgery employing such means. With the recent introduction however of compound E (17-hydroxy-11-dehydrocorticosterone) and adrenocorticotropin, it is anticipated that in the future, surgery for these tumors will be safer. It is now our policy to administer adrenocorticotropin preoperatively in order to stimulate the contralateral atrophic adrenal in spite of the risk of stimulating malignant tissue and of interfering with wound healing. Postoperatively both adrenocorticotropin and cortisone are concomitantly administered in order to stimulate the contralateral adrenal to produce adrenal cortical hormone and also to provide specific therapy in adequate dosage even if the adrenal cortical response to the pituitary fraction is inadequate. Later, cortisone and subsequently ACTH are gradually withdrawn thus permitting the endogenous production of ACTH to be resumed.

The interference with wound healing caused by the glycogenic steroids so well illustrated in this patient has recently been reproduced experimentally by Ragan and his associates.[41]

SUMMARY

A surgical cure of Cushing's syndrome due to benign adrenal cortical tumor is reported. The problem involved in diagnosis and management are discussed in the light of present day physiological knowledge.

17 E. 96 St. (G.D.O.) and 2 W. 82 St. (J.L.G.), New York City, N.Y.

[41] Ragan, C., Grokoest, A. W. and Boots, R. H.: Am. J. Med., 7: 741, 1949.

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THE DISTRIBUTION OF RENAL ISCHEMIA PRODUCED BY EPINEPHRINE AND NOR-EPINEPHRINE AS DEMONSTRATED BY THE FLUORESCENT DYE VASOFLAVINE*

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Renal ischemia is believed by a number of investigators[1, 2, 3, 4, 5] to be a factor in the production of acute renal failure in crushing injuries, shock, burns, transfusion reactions, and other conditions of similar character. This condition is often referred to as "lower nephron nephrosis"; a term which is quite misleading since the renal damage is not necessarily confined to the lower portion of the nephron.[5, 6, 7, 8] In these as well as in other conditions associated with shock, there is an increase in circulating epinephrine and nor-epinephrine.[9, 10]

Studies relating to the circulation of the kidney with an intact vascular system are relatively rare; the work of Trueta et al.[11] being a noteworthy exception. Attention in the past seems to have been focused mainly upon the response of isolated vessels or perfused organs to epinephrine and nor-epinephrine.[12, 13] The methods hitherto available for the study of the renal vessels have not been entirely satisfactory. Most of these methods, such as the quartz rod technique of Knisley,[14] and India ink injection, have involved the undesirable factors of a disturbance of tissues, vascular reactions caused by manipulation, toxic side effects from large doses of dye, and abnormal injection pressures.

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* A derivative of Thioflavine-S, available from National Aniline Division, Allied Chemical and Dye Corporation.

Buswell Fellow in Urological Research.

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Note by editor. Dr. Moses's paper was selected to be the Elmer Hess Prize essay, an award made by the Northeastern Section for the best manuscript submitted by a resident urologist and younger men practicing urology not more than two years, for presentation at the annual meeting of the section at the Lake Placid Club, Essex County, New York, September 19-22, 1951.

[1] Lucké, B.: Lower nephron nephrosis. (The renal lesions of the crush syndrome, of burns, transfusions, and other conditions affecting the lower segments of the nephrons.) Mil. Surg., **99:** 371, 1946.

[2] Snyder, H. E. and Culbertson, J. W.: Pigment nephropathy in battle casualties. Arch. Surg., **56:** 651, 1948.

[3] Maegraith, B. G., Havard, R. E. and Parsons, D. S.: Renal syndrome of wide distribution induced possibly by renal anoxia. Lancet, **2:** 293, 1945.

[4] Foy, H., Altman, A., Barnes, H. D. and Kondi, A.: Anuria, with special reference to renal failure in blackwater fever, incompatible transfusions, and crush injuries. Tr. Roy. Soc. Trop. Med. & Hyg., **36:** 197, 1943.

[5] Moon, V. H.: Origin and effects of anoxia. Bull. New York Acad. Med., **26:** 361, 1950.

[6] Moon, V. H.: Hemoglobinuric or tubular nephrosis (acute parenchymatous nephritis). North Carolina M. J., **9:** 238, 1948.

[7] Smith, H. W.: The Kidney. (Structure and Function in Health and Disease). New York: Oxford Univ. Press, 1951.

[8] Martineau, P. C. and Hartman, F. W.: The renal lesions in extensive cutaneous burns J. A. M. A., **134:** 429, 1947.

[9] Selye, H.: Textbook of Endocrinology. Montreal: Acta Endocrinologica Inc., 2nd ed. p. 128.

[10] Wiggers, C. J.: Physiology of Shock. New York: Commonwealth Fund, 1950, pp. 11 and 430.

[11] Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. and Pritchard, M. M. L.: Studies of the Renal Circulation. Springfield, Ill.: Chas. C. Thomas, 1947.

[12] Burn, J. H. and Hutcheon, D. E.: The action of nor-adrenaline. Brit. J. Pharmacol., **4:** 373, 1949.

[13] Hartman, F. A. and Brownell, K. A.: The Adrenal Gland. Philadelphia: Lea and Febiger, 1949. p. 151 ff.

It was decided to study the effect of epinephrine and nor-epinephrine upon the renal circulation by a method introduced by Schlegel[15] and modified by Moses, Emery, and Schlegel,[16] which eliminates these undesirable conditions and produces a more physiological picture of the blood distribution of an organ. This method is based upon the affinity of the fluorescent dye vasoflavine* for the walls of the blood vessels.

This dye is prepared by extracting the commercial dye thioflavine-S with distilled water. Only minute quantities in the tissues are required for visualization since it is brilliantly fluorescent in ultraviolet light. In the test tube when examined under ultraviolet light a solution of 500 mg. per cent fluoresces yellow-orange, a solution of 50 mg. per cent fluoresces yellow-green, while a solution of 5 mg. per cent fluoresces blue-violet. The difference in this fluorescence and its significance is discussed at length in a previous publication.[16] The 16 per cent solution which is commonly used for in vivo studies and which is near the point of saturation, imparts a yellowish-green fluorescence to the vessel walls when exposed to ultraviolet light. Unlike most fluorescent dyes it diffuses slowly out of the vessels into the surrounding tissues. It may therefore be injected into a peripheral vessel and reach the desired organ in sufficient concentration to be well visualized; thus eliminating the undesirable manipulation of vessels and pressure injection near the site of the tissues to be studied. The dye is nontoxic, nonirritating, and produces no vascular response in experimental animals even in concentrations as high as 275 mg. per cent in the blood.[17] Its property of being rapidly cleared from the blood and fixed in the intima of the vessel walls assures that only those vessels which are actually carrying blood at the time of injection will be outlined by the dye, and that manipulation and squeezing of the tissues during removal of the organ and its handling prior to examination will not in any way alter the true picture of the circulation at the time of injection.

METHOD

White male rabbits were used as the experimental animals. To establish the optimal dosage of epinephrine, fifteen rabbits were subjected to varying dosages of the drug (suprarenin†) and the duration of renal ischemia measured. A dosage of 35 micrograms per kilogram of epinephrine intravenously was chosen to work with since it was sufficient in this group to produce complete renal ischemia in rabbits for a period of at least one minute.

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[14] Knisely, M. H.: A method of illuminating living structures for microscopic study. Anat. Rec., 64: 499, 1936.

[15] Schlegel, J. U.: Demonstration of blood vessels and lymphatics with a fluorescent dye in ultraviolet light. Anat. Rec., 105: 433, 1949.

[16] Moses, J. B., Emery, A. J., Jr. and Schlegel, J. U.: A study of a purified fraction of thioflavine-S (vasoflavine): A valuable agent for visualization of blood vessels. Proc. Soc. Exper. Biol. & Med., 77: 233, 1951.

[17] Algire, G. H. and Schlegel, J. U.: Circulatory reactions in photodynamic action. J. Cell & Comp. Physiol., 35: 95, 1950.

* Available from National Aniline Division, Allied Chemical and Dye Corporation.

† Winthrop Chemical Co., Inc.

The following technique was employed: The animal was anesthetized by an intravenous injection of a solution of nembutal, 60 mg. for every 5 pounds of body weight, and the abdomen opened using a small transverse incision. Hemostasis was secured and the wound was then held closed with small bulldog clips. The animal was then allowed to remain undisturbed for a period of half an hour in order to recover from the immediate effects of surgery. Thirty-five micrograms per kilogram of epinephrine was then injected into an ear vein at a fairly rapid rate. Timing was started at the onset of the injection, and after the selected interval had elapsed, vasoflavine, 1 cc per kilogram of body weight of a 16 per cent solution, was injected intravenously at the same site and the kidneys removed between 10 and 15 seconds after the injection of the dye.

After the kidneys were removed they were sliced with a sharp knife and blotted on a lintless cloth or filter paper to remove any excess blood. These were then placed in glycerine U.S.P. The glycerine clears the tissue and slows down postmortem diffusion of the dye. Such specimens remain in good condition for at least an hour. The sections were examined microscopically under ultraviolet light, and photographs were made for a permanent record. Photographs may be made at any time within an hour after removing, but are best when done during the first 10 minutes.

TABLE 1. *Degree of renal ischemia in rabbits which received epinephrine, 35 micrograms per kilogram of body weight, at the three time intervals noted below*

GROUP	NO. OF ANIMALS	INTERVAL	RESULT
A	8	Control—no epinephrine	No ischemia
B	5	1 minute	Complete ischemia
C	9	1½ minutes	Partial ischemia
D	5	2 minutes	No ischemia

OBSERVATIONS

For the first series of observations of renal ischemia 27 animals were used. In group A, the control group, 8 animals were given vasoflavine, 1 cc per kilogram of body weight, according to the above procedure but without previous epinephrine injection (table 1, A). In all these animals there was an even distribution of dye throughout the glomeruli and vessels of the kidneys with no evidence of spottiness (fig. 1). In addition to this control group we have not observed any spotty distribution in over 100 normal animals used in perfecting this dye method.

Five rabbits were studied in group B, with an interval of one minute between the injection of epinephrine (35 micrograms per kilogram of body weight) and the injection of the dye (table 1, B). In all 5 there was complete renal ischemia as evidenced by the absence of fluorescent dye from the sections. Only the natural, greenish-yellow fluorescence of the kidney could be seen (fig. 2).

The third group of 9 rabbits (table 1, C) received identical treatment except that the interval between epinephrine injection and the injection of dye was increased to 1½ minutes. In all 9 of these animals there was a spotty distribution of dye in the kidneys, characterized by scattered groups of fluorescent glomeruli and vessels in an otherwise nonfluorescent kidney. The reverse has also been observed, that is, scattered areas of varying size in which there was no dye in an otherwise fluorescent organ (fig. 3).

The fourth group of 5 animals (table 1, D) received the same treatment except that the interval was increased to 2 minutes. In all these animals there was no evidence of any renal ischemia. All vessels and glomeruli were brilliantly fluorescent (fig. 4).

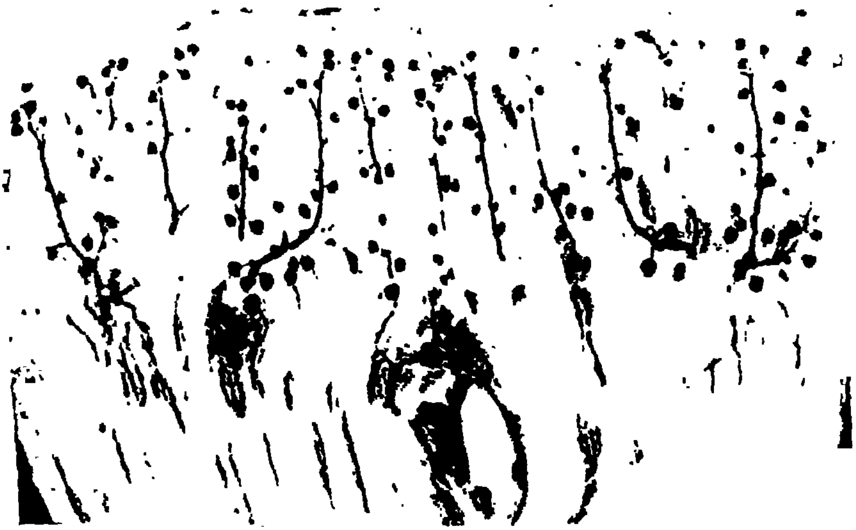

FIG. 1. Photomicrograph of kidney of rabbit in which only vasoflavine has been injected. No evidence of renal ischemia. (Taken in incident ultraviolet light.) (From group A, table 1.)

The lesions seen in the kidneys of cases with acute renal failure following crushing injuries, burns, transfusion reactions, etc., have been described in the literature as being irregular in distribution throughout the organs. Bywaters, who revived interest in the syndrome, describes them as focal areas of necrosis.[18]

Our attention was drawn to the similarity between the spotty ischemia following epinephrine injection and the focal necrosis in this type of kidney pathology. This has also been emphasized by Oliver.[19]

From our observations it seems reasonable to conclude that all vessels of the kidneys are not sensitive to epinephrine to the same degree, at the same time. Furthermore the recovery from the vasoconstrictive effects of epinephrine is more delayed in some areas than in others.

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[18] Bywaters, E. G. L.: Discussion on the effects on the kidney of trauma to parts other than the urinary tract, including crush syndrome. Proc. Roy. Soc. Med., 35: 321, 1942.

[19] Oliver, Jean: Personal communication, material to be published.

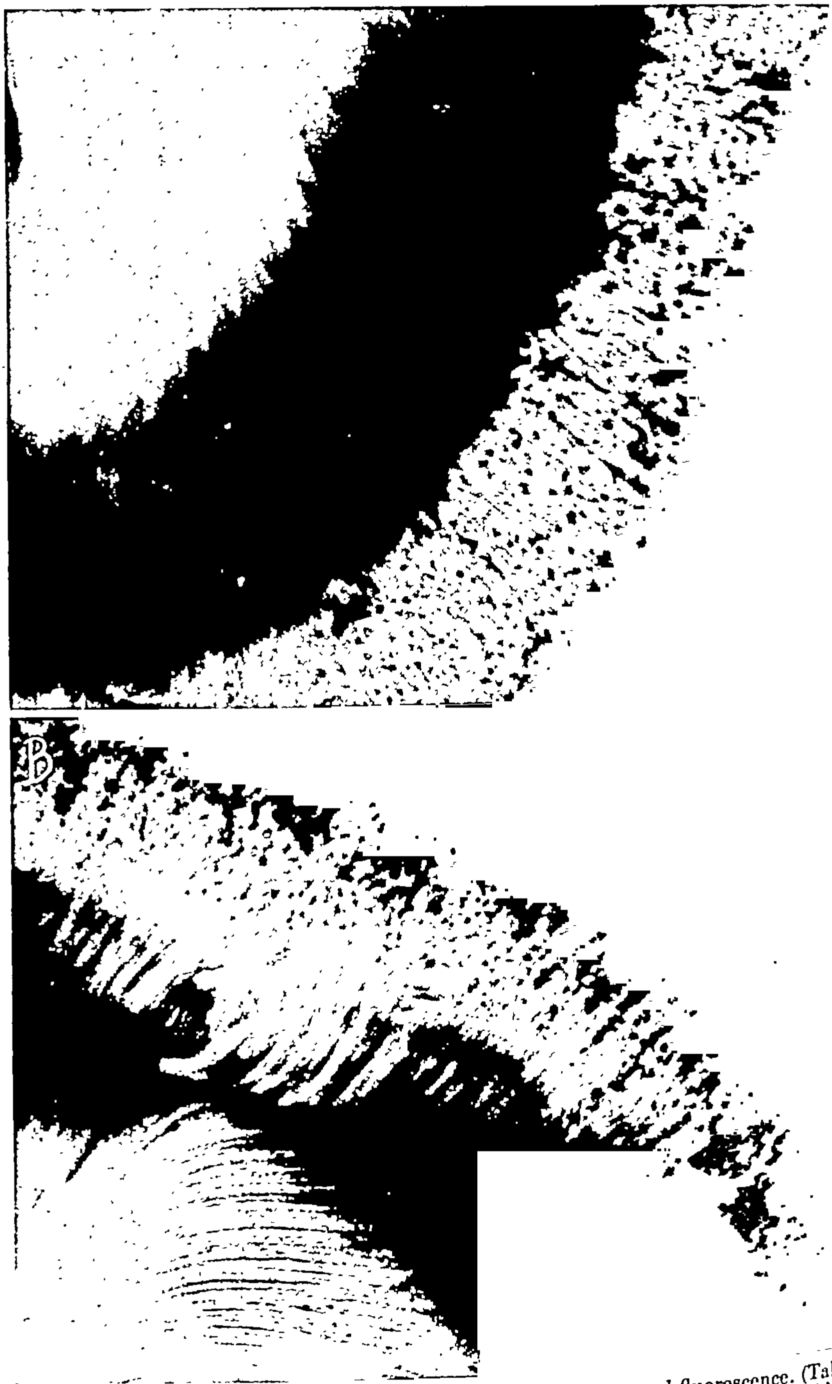

FIG. 2. *A*, photomicrograph of kidney of rabbit showing natural fluorescence. (Taken in incident ultraviolet light.) No dye has been injected. ×12. *B*, photomicrograph of kidney of rabbit in which both epinephrine and vasoflavine have been injected but in which there is complete renal ischemia. (Taken in incident ultraviolet light.) (From group B, table 1.) ×12

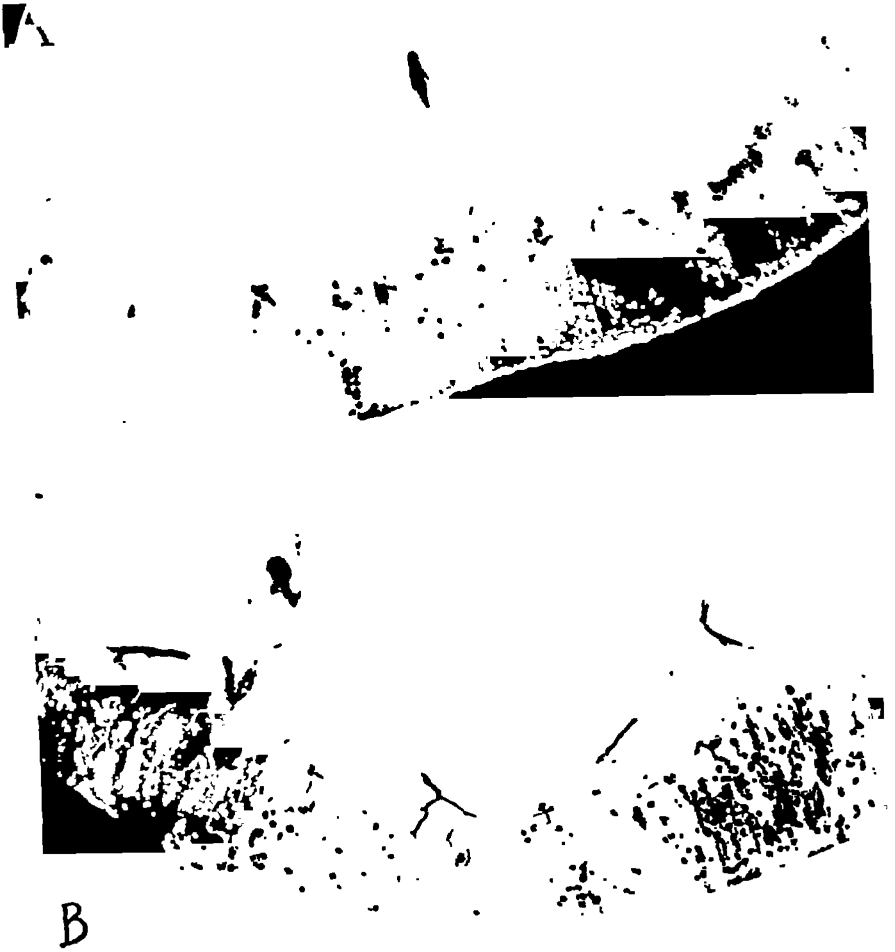

FIG. 3. *A* and *B*, photomicrographs of kidney of rabbit showing two types of dye distribution in partial renal ischemia. (Taken in incident ultraviolet light.) (From group B, table 1.) ×12.

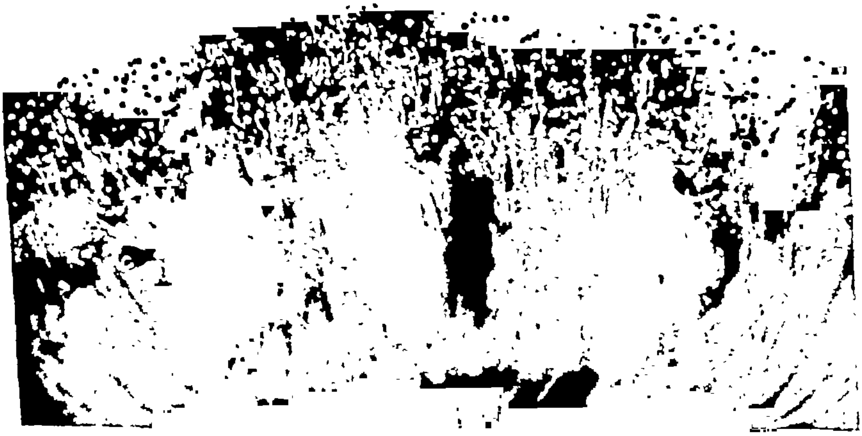

FIG. 4. Photomicrograph of kidney of rabbit in which both epinephrine and vasoflavine have been injected, but in which there is no evidence of renal ischemia. (Taken in incident ultraviolet light.) (Group group D, table 1.) ×12

The question is now raised: Can we assume that the ischemia produced by these relatively high doses of epinephrine bears any resemblance to that which might be produced in the organism under physiological conditions? Accordingly in a group of 5 animals (table 2, A) the dosage of epinephrine was lowered to 0.5 micrograms per kilogram of body weight which probably more nearly approaches the physiological level.[9] The time interval was reduced to 30 seconds since this was the borderline interval for the production of renal ischemia with this dosage. As can be seen in table 2, A, there is an individual variation between animals under exactly the same conditions. Partial ischemia occurred in two animals while in the others no ischemia was produced.

TABLE 2. *Degree of renal ischemia in rabbits which received epinephrine 0.5 micrograms per kilogram of body weight, and a time interval of 30 seconds*

EXPT. NO.	ANIMAL	DCA	ISCHEMIA
		Group A	
1	416	None	None
2	419	None	Partial
3	402	None	None
4	467	None	Partial
5	464	None	None
		Group B	
6	397	1 mg. daily × 19	Partial
7	398	1 mg. daily × 20	Partial
8	400	1 mg. daily × 22	None
9	412	1 mg. daily × 25	None
10	410	1 mg. daily × 26	Partial

Note that group A did not receive any desoxycorticosterone acetate (DCA) while group B received pre-treatment with DCA 1 mg. daily intramuscularly for the period noted above.

That the variability in the response of these animals to epinephrine is a result of the variation in the animal's own production of epinephrine or that it is dependent upon other factors produced by the animal which might sensitize it to epinephrine are both possibilities to consider.

It has been observed by Raab,[20] Raab, Humphreys and Lepeschkin[21] and others cited by them that in normotensive human subjects the pressor effect of subcutaneously administered epinephrine, infusions of epinephrine, or nor-epinephrine were significantly intensified after several days of pretreatment with daily doses of 10 mgs. of desoxycorticosterone acetate (DCA) intramuscularly. Selye[22] has described definite vascular changes and hypertension following prolonged administration of it.

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[20] Raab, W.: Cardiovascular effects of desoxycorticosterone acetate in man. Am. Heart J., 24: 365, 1942.

[21] Raab, W., Humphreys, R. J. and Lepeschkin, E.: Potentiation of pressor effects of nor-epinephrine and epinephrine in man by desoxycorticosterone acetate. J. Clin. Investigat., 29: 1937, 1950.

These investigations seemed to lend support to the idea of a difference in the sensitivity towards epinephrine depending upon adrenal cortical activity. Consequently another group of 5 male rabbits was selected and to each of them was administered 1 mg. of DCA in oil* intramuscularly daily for 19, 20, 22, 25, and 26 days respectively (table 2, B). At the end of each period the animal was subjected to the same procedure as outlined above. An interval of 30 seconds between injection of epinephrine and vasoflavine was selected, and the dosage of epinephrine was 0.5 microgram per kilogram of body weight. Partial renal ischemia was produced in 3 of the 5 animals. Since in group A, to which no DCA was administered, partial ischemia was produced in 2 of the 5 rabbits, we can only conclude that no significance can be attached to this increase and that we could not consistently augment the action of epinephrine by DCA.

TABLE 3. *Effects of epinephrine and nor-epinephrine on renal ischemia and blood pressure in rabbits treated with desoxycorticosterone glucoside (DCG)*

EXPT. NO.	ANIMAL	DCG	EPINEPHRINE	NOR-EPINEPHRINE	ISCHEMIA	BLOOD PRESSURE RESPONSE
			Group A			
1	422	1 mg.	0.5 γ/kg.		None	No significant change
2	423	1 mg.	0.5 γ/kg.		Partial	Prolonged
			Group B			
3	466	5 mg.		35 γ/kg.	None	Definitely prolonged
4	468	5 mg.		35 γ/kg.	Partial	Definitely prolonged
5	470	5 mg.		35 γ/kg.	None	Definitely prolonged
6	455	5 mg.		35 γ/kg.	None	Shortened
7	472	5 mg.		35 γ/kg.	None	Slightly prolonged

In group A, 1 mg. of desoxycorticosterone glucoside (water soluble) was given in 100 cc of 5 per cent dextrose solution over a period of 1½ hours. In these experiments epinephrine was used. In group B, 5 mg. of DCG was given in 50 cc of 5 per cent dextrose solution over a period of 45 minutes. In this group nor-epinephrine was used.

In order to evaluate further this blood pressure change, 2 rabbits were subjected to the same procedure outlined above for the DCA animals except that blood pressure tracings were made by means of a manometer connected with a cannula in the right carotid artery, before and after an infusion of 5 per cent glucose containing 1 mg. of water soluble desoxycorticosterone glucoside† given over a period of 1½ hours. The results as outlined in table 3, A show that there was no ischemia in the first animal and no definite prolongation of the epinephrine response. The second rabbit exhibited a more prolonged elevation of blood pressure and a partial ischemia.

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[22] Selye, H. Stress. Montreal: Acta Endocrinologica Inc., 1950, pp. 533 and 569.
* Percorten, furnished through the courtesy of Ciba Pharmaceutical Laboratories.
† Furnished through the courtesy of Ciba Pharmaceutical Company, Inc.

To avoid the untoward effects of repeated injections of epinephrine, chief of which is pulmonary edema and hemorrhage, 1-nor-epinephrine (Levophed*) was substituted. It was found that, for the purpose of causing renal ischemia, its effect did not seem to vary in type from that of epinephrine. Nor-epinephrine could be injected every 15 minutes in rather large doses over a period of several hours without adverse effects. The dosage of nor-epinephrine was set at 35 micrograms per kilogram. The dosage of desoxycorticosterone glucoside was increased to 5 mg. and was given intravenously in 50 cc of 5 per cent glucose solution in a drip over a period of 45 minutes (table 3, B). No significant change was seen in the amplitude of the response to nor-epinephrine, but it will be seen that the pressor effect was subject to variation from definite prolongation to actual curtailment in one animal.

From the data compiled from this group of experiments the sensitization of the renal vessels to epinephrine by desoxycorticosterone is by no means borne out with consistency. However variation in the results points against a direct effect of desoxycorticosterone but rather an indirect one, if any.

DISCUSSION

It is well known that prolonged ischemia causes necrosis. Ischemia of short duration might render an organ more liable to the action of toxic substances. Such a mechanism may well play an important role in the production of kidney damage in cases of crush injuries, burns, transfusion reactions, etc., where the toxic agent is generally supposed to be hemoglobin or myoglobin or their derivatives.

The data presented seem to lend support to the idea that the spotty appearance of the renal vascular changes following crushing injuries, burns, transfusion reactions, etc. may in part be explained in terms of the spotty renal ischemia which can be produced by injections of epinephrine and nor-epinephrine. This can be brought about either by an increase in the release of epinephrine during the injury or during the state of shock which follows, or by an increased sensitivity to these sympathomimetic agents. Since DCA is a synthetic preparation it does not necessarily follow that the inconsistent results of our experiments rule out any role of the adrenal cortex. In shock there is an increase in the output of epinephrine and furthermore there is also an increase in the production of cortical hormones,[23] so that both factors may play a role in the production of renal ischemia. The difference in effect of injected epinephrine in equal dosages might well depend, not only upon the variation in the adrenergic tonus, but also upon changes in adrenal cortical activity, probably mediated through a variation in the activity of the anterior lobe of the hypophysis. The reason for the spotty appearance of the ischemia is difficult to explain. However, it seems most reasonable to assume that the differences in response to epinephrine could be due to purely local factors.

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* Furnished through the courtesy of Winthrop-Stearns, Inc.

[23] Long, C. N. H.: The conditions associated with the secretion of the adrenal cortex. Federation Proc., 6: 461, 1947.

SUMMARY

The production of renal ischemia in the intact animal with epinephrine and nor-epinephrine has been demonstrated by the use of a fluorescent dye, vasoflavine.

The similarity in distribution of the partial renal ischemia to that of the renal necrosis resulting from cases of crush, transfusion reactions, burns, and similar conditions resulting in shock has been pointed out.

The role of the adrenal cortex in conditioning the response of the renal circulation to epinephrine has been briefly discussed in the light of a series of experiments involving the administration of both desoxycorticosterone and epinephrine and nor-epinephrine.

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NEPHRECTOMY FOR TUBERCULOSIS

NATHAN CHASET

The use of streptomycin in the treatment of tuberculosis of the genito-urinary tract has been most encouraging. Lattimer and his associates[1, 2] have shown remarkable results with this drug and also have hinted at even more remarkable results to come by using streptomycin in conjunction with other drugs. The action of streptomycin alone or streptomycin together with various other drugs has been extremely efficacious as far as present results are known. As Huffines and Weber[3] have stated: "The last word on chemotherapy of tuberculosis has not been said; much has already been done; and research in some of the newer antibiotics has been very promising." Others[4, 5] have been equally enthusiastic and have reported very satisfactory results. There is also a good deal of evidence which points to the fact that streptomycin is not yet a cure-all and that there are certain cases in which streptomycin apparently does very little good. Rinker[6] has recently reported 5 cases treated with streptomycin in which the previously passable ureter has become impassable or occluded after streptomycin therapy. Nephrectomy had to be done in all of these cases. Nesbit, and Bohne[5] also mention this complication in one of their cases. Certainly the results here are not to be considered as satisfactory.

Oppenheimer and Narins[7] recently reviewed 117 cases of renal tuberculosis at Mt. Sinai Hospital of which 106 had nephrectomy for unilateral renal tuberculosis. Their figures show an appreciable number of patients surviving 15 years or over after nephrectomy and these patients are to be considered cured. The patients with a shorter period of follow-up show evidence of good results and good life expectancy. They conclude that "for the present time, nephrectomy for unilateral renal tuberculosis has proven to be a time-tested and efficacious method of treatment. Until a long-followed series of cases treated solely with streptomycin can be shown to compare favorably with surgically treated cases, nephrectomy for unilateral renal tuberculosis, perforce, must be regarded as a reliable method of treatment."

This paper does not intend to discuss the merits of one form of therapy over another. The judicious use of both methods, singly or together, will eventually crystallize our thinking on this subject with resulting benefit to all our patients. I am attempting to present here a technique for nephrectomy for tuberculosis which eliminates some of the hazards and complications of the procedure and also in most cases obviates the necessity for extensive surgery in a weak, debilitated patient.

It has been generally accepted that a kidney badly diseased with tuberculosis

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[1] Lattimer, J. K., Amberson, J. B. and Braham, S.: J. Urol., **62**: 875–888, 1949.
[2] Lattimer, J. K. and Amberson, J. B. et al.: J. Urol., **60**: 974–981, 1948.
[3] Huffines, T. R. and Weber, W. D.: J. Urol., **62**: 862–872, 1949.
[4] Slotkin, G. E.: J. Urol., **58**: 464–478, 1947.
[5] Nesbit, R. M and Bohne, A. W.: J. A. M. A., **138**: 957, 1948.
[6] Rinker, J. R.: J. A. M. A., **142**: 87, 1950.
[7] Oppenheimer, G. and Narins, L.: J. Urol., **62**: 804–806, 1949.

should be removed. There has been, however, a good deal of discussion concerning the handling of the ureter. Total nephro-ureterectomy has been a method advocated by many for the badly diseased kidney and ureter. This is an extensive operation for a weak and debilitated patient and it is also doubtful in many cases that the entire ureter can be removed. In *Young's Practice of Urology,*[8] it is stated that "in some cases the adhesions to the seminal vesicle, vas, rectum and pelvic cellular tissues are so great that the point of division is necessarily remote from the bladder." In these cases the terminal portion may drain into the deep pelvic tissues and may even be the source of a miliary tuberculosis.

Nephrectomy with ligation of the ureter with carbolization of the cut end of the ureter is also done. This potentially infects the area and wound breakdown may follow. Bidgood quoted by Young and Davis[8] showed an 18 per cent breakdown of wounds following nephrectomy for tuberculosis. Some, of course, must be attributed to initial soiling of the wound by tuberculous pus during the nephrectomy.

Nephrectomy with a later ureterectomy to cure persistent ureteral sinuses has been done. This would indicate clearly a failure to cure by the nephrectomy alone.

Nephrectomy and then bringing the ureter out through the lower angle of the incision or through a separate stab wound has also been advocated.[9]

Other methods have been advocated, usually after long experience with persistent sinuses or widely gaping infected wounds. Greenberger and Helfert[10] outlined many therapeutic agents used for sinus and gaping wounds and stated "each being associated with occasional success."

The technique described here is intended to obviate as much as possible the undesirable postoperative complications which have hitherto been of such distress to both patient and surgeon. The number of cases done has been small, but the results have been so uniformly good and without complications of any kind that I have been impelled to present this technique.

The usual lumbar approach is made in the usual manner. In freeing the kidney no attempt is made to clean the kidney, but as much of the perirenal fat as is feasible is left attached to the capsule. The ureter is also freed from its bed with peri-ureteric tissue adherent and again no attempt is made to clean the ureter. The ureter is freed down to the sacral area to obtain as much length as is necessary to bring the ureter out anteriorly without tension. The vascular pedicle is then clamped, cut, and tied in the usual manner without severing the ureter. The kidney with ureter still intact is then brought out through the anterior end of the incision. It should lie outside the incision without undue tension on the ureter. If this is not so, the anterior end of the incision may be lengthened in the proper direction to obtain the desired result. The ureter is then fixed to the transversalis fascia with fine silk sutures on French spring-eye needles, care being taken not to enter the lumen of the ureter. The incision is closed in the usual manner and

[8] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926.

[9] Hess, E. Cyclopedia of Medicine (Piersol). Philadelphia: F. A. Davis Co., 1950.

[10] Greenberger, M. E. and Helfert, I.: Am. J. Surg., 51: 396–398, 1941.

the ureter is again fixed to the skin with fine silk sutures. At this stage the kidney and ureter are still intact and no opening has been made into any portion of the drainage system. Nor has one drop of urine been spilled. The incision is then well covered with dressings and a vaseline gauze strip placed around the ureter. The entire dressing is covered with adhesive so that a relatively non-porous cover is over the entire dressing. The ureter is then severed high up near the ureteropelvic junction and the kidney removed. A separate vaseline dressing is applied to the stump, and this dressing may be changed as often as necessary.

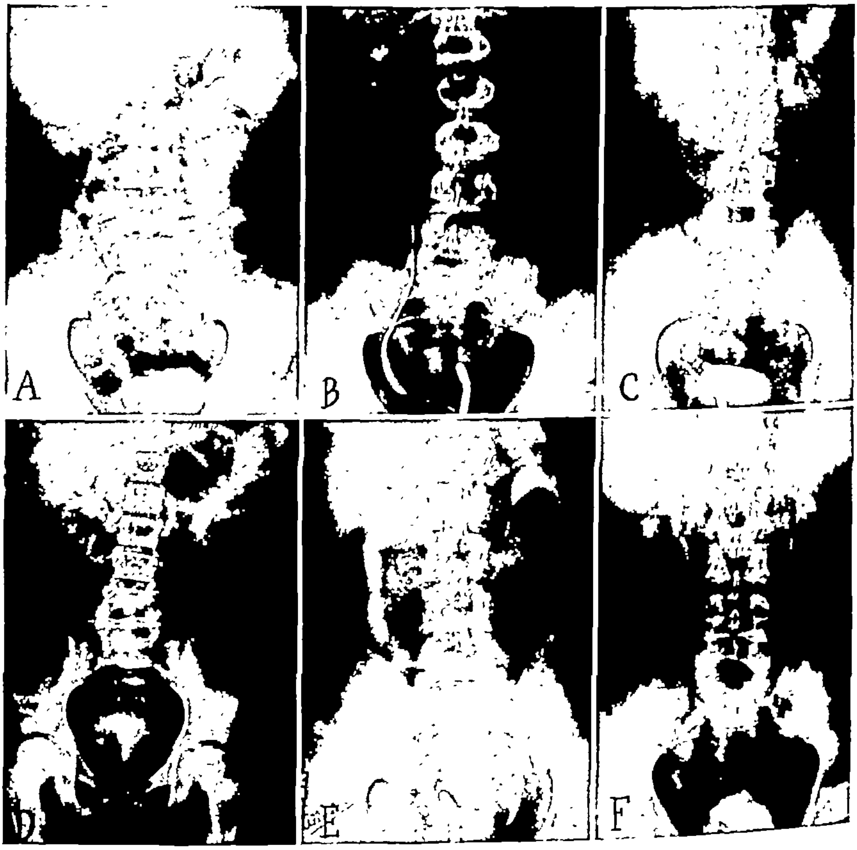

FIG. 1

CASE REPORTS

The following cases have been treated by the foregoing method.

Case 1. R. I. H. No. 408085, a 19-year old white man entered the hospital June 7, 1946. He was well until 2 years before entry when he began to note frequency, nocturia and burning and on three occasions had gross hematuria with clots. His father had died of tuberculosis 13 years previously. The patient had been told that he had "spots on his lungs" 1½ years before entry and had been followed in a tuberculosis clinic. Physical examination was negative. Blood pressure 118/78. Urinalysis: 35–40 red blood cells and 2–3 white blood cells per high powered field; specific gravity 1.015; pH 7.0; protein trace; sugar 0. Blood urea nitrogen 9 mg., glucose 67. White blood count 9,500, normal differential. Hinton test was negative. A chest x-ray showed caps of old pleural thickening at both apices. The lung fields were otherwise clear. A smear of the urine sediment showed acid-fast organisms, and guinea pig and acid-fast culture were both positive. An excretory urogram done showed lack of function on the right with probable tuberculosis. The left kidney was normal (fig. 1, *A*). The bladder was somewhat small and somewhat distorted, consistent with tuberculosis. A right nephrectomy was done according to the technique described. Recovery was uneventful. The pathologic report was tuberculosis of right kidney. The patient was discharged on July 6, 1946. The urine cleared rapidly and remained so.

Case 2. R. I. H. No. 416440, a 17-year old white man, entered the hospital on January 29, 1947. He had a history of 3 months' duration of frequency, nocturia and unexplained low-grade fever. He had also noted easy fatiguability, loss of appetite, and weight loss. There was no previous history of tuberculosis in the family or in the patient. Physical examination was negative. Urinalysis: pH 5.0; specific gravity, 1.010; protein, 2 plus; sugar, negative. The sediment showed 4–5 red blood cells per high powered field and loaded with white blood cells. A smear of the sediment was positive for acid-fast organisms. The blood urea nitrogen was 14, glucose 87. Hinton test was negative. Guinea pig and acid-fast culture were both positive. An excretory urogram before admission showed tuberculosis of the left kidney (fig. 1, *B*). The right side was apparently normal. Cystoscopy showed the left orifice very edematous and two definite tubercles about the orifice. On February 5, 1947 a left nephrectomy was done according to the technique described. Streptomycin 2 gm. daily was given postoperatively. The pathologic report was tuberculosis of the left kidney. Convalescence was uneventful. The patient was discharged February 14, 1947. The urine cleared rapidly and has remained clear until present time.

Case 3. R. I. H. No. 428849, a 42-year old white man entered the hospital for the third time. The first admission was for cystoscopy and retrograde pyelograms. These showed obstruction at lower end of right ureter with dilatation above (fig. 1, *C*). The left was normal. Cultures taken from the left kidney were also positive for tuberculosis, probably due to contamination from the bladder. Accordingly the patient was re-admitted for another check-up. The left catheter was passed while a constant stream of water was being injected through the catheter until the catheter passed through the orifice. In this way it was hoped that bladder contamination would be eliminated. The urine obtained showed no puss cells or organisms. Culture was negative.

The patient was again admitted on December 12, 1947 and a right nephrectomy was done by the method described here. Streptomycin 2.0 gm. daily was given postoperatively. The pathologic report was tuberculosis of the right kidney. Patient discharged on December 24, 1947. Convalescence was uneventful until about 6 months postoperative when patient complained of pain and swelling in the area where ureteral stump was brought out. This opened spontaneously and drained for about one week. It then closed and has remained closed and dry ever since. Urine cleared rapidly and has remained clear.

Case 4. R. I. H. No. 442001, a 8-year old girl was admitted on November 16, 1948 as a transfer from the R. I. State Sanatorium at Wallum Lake. The child had known pulmonary tuberculosis at age 1½. The right upper lobe was involved. She also had involvement of the tenth and twelfth thoracic vertebrae. The urine was positive for tuberculosis. One and one-half years before admission the urine was positive for tuberculosis. Streptomycin was given for total dose of 40 gm. Six months later guinea pig examinations were still positive. An excretory urogram showed a large nonfunctioning left kidney (fig. 1, *D*). Sputum examinations and chest x-rays were now negative. The blood pressure was 106/60. The child was well-developed and well-nourished. Urinalysis: Specific gravity, 1.020; pH 8.0; protein 1 plus; sugar, 0; sediment showed 20–25 red blood cells per high powered field and a rare red blood cell. The blood urea nitrogen was 11; red count 3.92 million and white count 5,7000; hemoglobin 11.2 gm. Urine culture was positive for acid-fast organisms. On November 29 a left nephrectomy was done according to the technique described. Pathologic diagnosis was tuberculosis of the left kidney. Convalescence was uneventful and the incision healed without event. Postoperatively patient received 0.25 gm. dihydrostreptomycin every 6 hours. Urine remained cloudy and a later report from the sanatorium indicates that patient now probably has tuberculosis on the other side.

Case 5. R. I. H. No 442025, W. A., a 36-year old white man entered the hospital on November 15, 1948 with a 2-year history of hoarseness. He was then found to have bilateral pulmonary tuberculosis and laryngitis. A routine urine showed many red blood cells and white blood cells and also acid-fast organisms. Excretory urography showed tuberculosis of the right kidney with an apparently normal left kidney. The patient was given a 5-month course of streptomycin with improvement in the hoarseness and cleaning of the chest lesions. Tuberculosis also developed in the right ankle. The left epididymis was suspicious of tuberculosis. Blood urea nitrogen, 8; red blood count 4.9 million; hemoglobin 14.9 gm.; white blood count, 8,300. On November 20, a bilateral pyelography was done. The right kidney was definitely tuberculous with stricture of right lower ureter (fig. 1, *E*). On November 24, a right nephrectomy was done according to the technique described. Pathologic report was tuberculosis of right kidney. Convalescence was entirely uneventful and the wound healed per primam. The patient received 0.5 gm. streptomycin q.i.d. postoperatively. This patient had a left orchiectomy done on April 16, 1949. Examination of the specimen showed tuberculosis. Urine cleared rapidly and has remained so.

Case 6. Miriam Hospital No. 3591, A. C., 50-year old man entered the hospital with history of fatigue, frequency, dysuria, and pain in right costovertebral angle. He later noted burning and pain at the end of urination. An excretory urogram showed tuberculosis of right kidney (fig. 1, *F*). A definite stricture of lower end of right ureter was found. Cultures and smears were positive for acid-fast organisms. On October 26 patient had a right nephrectomy done according to the technique described. Convalescence was uneventful and rapid. Urine cleared rapidly and has remained so.

COMMENT

A technique for nephrectomy for tuberculosis is presented which avoids spilling of infected urine into any portion of the wound. The necessity for extensive nephro-ureterectomy is also removed and the ureteral stump acts as its own safety valve and channels all infected material to the outside. This is extremely important in cases of tuberculosis with stricture of the vesical end of the ureter. In one of these 6 cases (case 3) there was apparently complete healing and then, 6 months later, the ureteral stump drained again, and then closed and has remained closed for over 2½ years. All other cases drained through the stump for varying periods, usually 2–3 weeks, and then closed and remained closed. No other wound complications have been encountered. Every wound healed per primam and they have remained as solid thin line scars. All patients apparently have been cured of the disease except case 4, in which there was very extensive tuberculosis and most likely bilateral tuberculosis at the time of operation. The child, however, is still alive and apparently doing well. Certainly, a nephrectomy done quickly and easily with no wound soiling and with quick and solid healing of her wound added considerably to her chances of survival. I believe that extensive nephro-ureterectomy with wound soiling might have been enough to make this a fatal case.

The technique is easy to perform, is not an extensive, exhausting procedure for patient or surgeon, and offers the patient a chance for cure of the disease with a minimum of complications.

This method could also be used in cases of severe pyohydro-ureter with stricture or obstruction at the vesical end. Again there would be no spilling of infected material into the wound and the ureteral stump would act to channel all debris to the outside and would act as a safety valve for future exacerbations.

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"ATRAUMATIC" NEPHROSTOMY

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The indications for nephrostomy are well established. The techniques of the operation are, however, not so well standardized and vary according to the purpose for which the nephrostomy is performed. The procedure described here has been developed for use in those situations in which it is desirable to place a catheter of large caliber through thick parenchyma and leave it in place for a considerable length of time.

Parenchymal damage and bleeding often accompany the insertion of the Cummings or Malecot catheters. This trauma is due in large measure to passing through the cortex either the head or the butt of the catheter, both of which are comparatively rough and of larger caliber than the mid-shaft portion of the catheter. The catheter herein described overcomes these disadvantages by having the last 6 inches of its butt end gradually tapered to a caliber of 10F. Kidney damage during the insertion of this catheter is, therefore, limited to that caused by the passage of a small Kimball hook through the cortex. The hook is guided through the calyx selected for nephrostomy by means of a finger introduced into the kidney through the pyelotomy. The tip of the hook is inserted into the tapered catheter tail. As the hook is withdrawn, the catheter is pulled into desired position. As this is done the tapered tail acts as a wedge to gradually enlarge the puncture-nephrotomy so that it snugly accommodates the shaft of the catheter. A small incision through the renal capsule at the site of nephrotomy will prevent "tenting" of the capsule as the catheter is pulled through. When in the desired position, the tail of the catheter is cut off, this provides a large lumen for the attachment of a drainage apparatus.

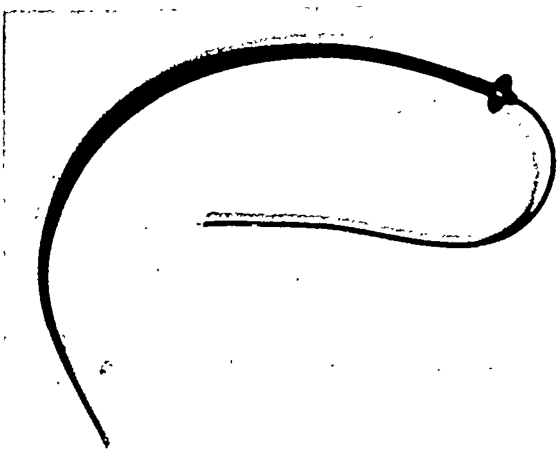

Fig. 1. Cummings nephrostomy catheter with butt tapered from 26F to 10F

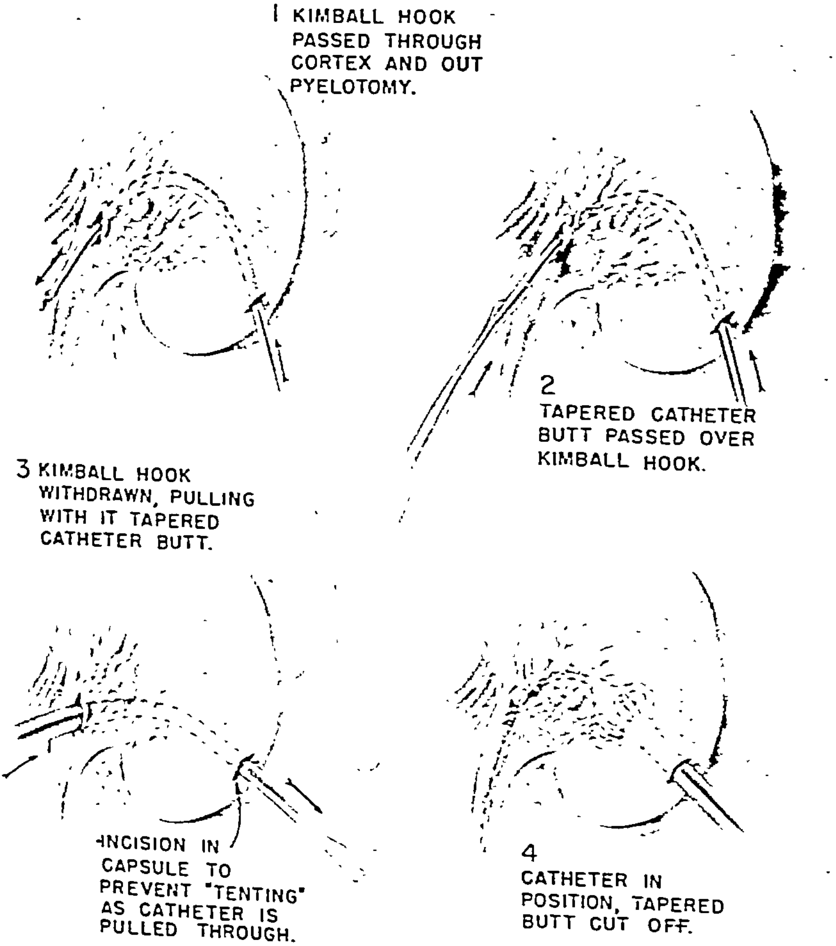
1 KIMBALL HOOK PASSED THROUGH CORTEX AND OUT PYELOTOMY.
2 TAPERED CATHETER BUTT PASSED OVER KIMBALL HOOK.
3 KIMBALL HOOK WITHDRAWN, PULLING WITH IT TAPERED CATHETER BUTT.
INCISION IN CAPSULE TO PREVENT "TENTING" AS CATHETER IS PULLED THROUGH.
4 CATHETER IN POSITION, TAPERED BUTT CUT OFF.

FIG. 2. Technique of introducing catheter

Attached to the head of the catheter is a splint for use in pyeloplasty or ureteroplasty. This splint is of such length that it can be passed into the bladder, thus preventing pressure damage of the ureter by its tip. If desired the splint may be cut to any length or removed entirely.

We have found the use of the wedge principle for insertion of nephrostomy catheters has reduced bleeding and parenchymal damage to a minimum.

Appreciation is expressed to Dr. John E. Dees, Associate Professor of Urology, for his helpful suggestions and to Mr. E. S. Outwin of C. R. Bard, Inc. for making the catheter available.

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CLEAR CELL CARCINOMA (HYPERNEPHROMA) OF THE KIDNEY WITH METASTASIS TO THE THYROID GLAND

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In 1948, Denton and McClintock[1] found reports of 21 cases of carcinoma of the kidney with metastases to the thyroid gland. These investigators emphasized the fact that, although most of the cases reported are based on necropsy studies, in 6 instances metastatic lesions developed in the thyroid gland 7 to 13 years after removal of renal tumor.

Recently attention has been focused on the excision of solitary metastases as well as the primary lesion in an attempt to cure malignant disease.[2] Barney[3] and Barney and Churchill[4] report a case in which a pneumonectomy was performed for a solitary lung metastasis one year after a nephrectomy for adenocarcinoma of the kidney. This patient was living and well 13 years later. Solitary lung metastases from other types of carcinoma have been operated upon by Deming and Lindskog,[5] Raine,[6] Effler and Blades,[7] and Blalock[8] with satisfactory results.

The following is a case report of a hypernephroma of the kidney with metastases to the thyroid gland treated by surgical excision of both the secondary and the primary lesions. It is now more than 2 years since operation and no other secondary lesions are demonstrable by either clinical or roentgenographic study.

CASE REPORT

A 57 year old white woman was admitted to the Cleveland Clinic Hospital January 6, 1949. Her chief complaints were enlarging goiter for 5 years and dyspnea for 1 year. Careful questioning revealed that, while the patient had had a goiter for 25 years, in the past few years the growth had enlarged significantly. Hypertension was first noted about 5 years prior to admission. In the past year the patient had lost 20 pounds despite a good appetite. She also complained of a sensation of pressure in her throat. Dyspnea on effort was experienced, as well as transient edema of the ankles.

One year prior to admission a mass was found in the left side of the abdomen but the patient declined diagnostic studies at that time. Because the goiter was asymptomatic the patient had refused thyroidectomy 5 years previously.

Physical examination revealed the blood pressure to be 220/128. Pulse rate was 112. The patient weighed only 90 pounds and the clinical appearance suggested hyperthyroidism. There was no exophthalmos. A large, hard, nodular goiter filled the neck and moved slightly on swallowing. The heart was enlarged and a blowing systolic murmur was present, most audible in the aortic area. Examination of the abdomen showed a firm oval mass about 7 cm. in diameter in the left upper quadrant which appeared to be movable. The liver was palpable 2 fingerbreadths below the costal margin.

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[1] Denton, G. R., and McClintock, J. C.: Ann. Surg., **129**: 390–403, 1949.

[2] Linton, R. R., Barney, J. D., Moorman, H. D. and Lerman, J.: Surg., Gynec. and Obst., **83**: 494–498, 1946.

[3] Barney, J. D.: J. Urol., **52**: 406–407, 1944.

[4] Barney, J. D. and Churchill, E. D.: Tr. Am. A. Genito-Urin. Surg., **31**: 71–79, 1938.

[5] Deming, C. L. and Lindskog, G. E.: J. Urol., **52**: 309–318, 1944.

[6] Raine, F. J.: Metastatic carcinoma of lung invading and obstructing bronchus. J. Thoracic Surg., **11**: 216, 1941.

[7] Effler, D. B. and Blades, B.: J. Thoracic Surg., **17**: 27–37, 1948.

[8] Blalock, cited by Effler and Blades.

The basal metabolic rate on January 6, 1949 was reported plus 76 per cent, the pulse rate varying from 108 to 132 during the test. Four days later it had fallen to plus 51 per cent. A tracer dose of radio-active iodine showed uptake of only 18 per cent in the thyroid area. There was no significant uptake over the tumor in the left upper quadrant. X-ray of the chest disclosed enlargement of the heart, but no evidence of metastatic tumors. Pyelogram showed deformity of the left renal pelvis and calcification of a mass. The findings indicated presence of a renal tumor, but it was decided to defer treatment of this tumor until thyroidectomy had been performed. Urinalysis showed 4-plus albumin, 1 to 3 red cells and 1 to 3 white cells per high-powered field. A cell block of sediment in the urine from the left ureter was reported as positive for cells compatible with malignancy. Blood sugar, blood urea, Wassermann and Kahn tests and blood counts were within normal limits.

Preoperative diagnosis was 1) carcinoma of the thyroid, 2) renal tumor, 3) essential hypertension and 4) probable hyperthyroidism, although the possibility was considered that the hypermetabolism might be the result of the hypertension.

On January 11, 1949 thyroidectomy was performed. The tumor was removed together with all of the thyroid except a minute amount of tissue at the upper pole. The tumor, which was encapsulated, did not invade the surrounding tissues at any point and was removed intact. Gross examination of the thyroid tumor showed a large oval encapsulated mass 8 by 8 by 5 cm., from one margin of which arose a nodular projection 5 by 3 by 3 cm. Sectioning of the mass revealed that the larger portion was adjoined by a second independent nodule of similar appearance. The tissue was soft, reddish brown, and contained many areas which resembled evidences of old hemorrhage, with irregular coarse grade trabeculae and cystic areas 0.2 to 0.4 cm. in diameter. The fibrous capsule surrounding the mass was calcified in several areas. A third smaller nodule resembled a benign adenoma of the thyroid. The paranodular thyroid tissue was normal in appearance.

Microscopic examination showed the tumor to be composed of large epithelial cells with sharp cell margins, clear cytoplasm, uniform round nuclei arranged in sheaths and with lumina containing blood. Mitoses were not recognized. The small nodule was a microfollicular adenoma of the thyroid. The paranodular thyroid tissue was composed of follicles of medium size with flat epithelium and well filled with colloid.

The convalescence from the thyroidectomy was uneventful. The patient's blood pressure fell from over 250/130 to 130/90. The basal metabolism, nevertheless, remained elevated 4 days after operation to plus 32 per cent. A week after the thyroidectomy a left nephrectomy was performed and the tumor was removed along with the kidney. Pathologic examination of the left kidney showed that it weighed 280 gm. and measured 14 by 8.5 by 4.5 cm. The neoplasm formed an irregularly lobulated mass projecting from one pole of the kidney; it appeared to be encapsulated except where it infiltrated the kidney substance and the gross appearance was similar to that of the thyroid tumor. Microscopically it was composed of sheets of clear cells with sharp cells margins, medium sized nuclei of uniform configuration and of round contour similar in every respect to those of the thyroid tumor. Blood vessel invasion was not apparent nor were mitotic figures demonstrated. Convalescence from this operation was also uneventful. The patient's metabolism remained at plus 21 per cent. The pulse rate had now fallen to as low as 80. The blood pressure remained at 130/90.

Two years and 6 months after nephrectomy and thyroidectomy, no palpable tumor was present either in the neck or the renal region. X-ray of the chest was negative. The patient weighed 21 pounds more than before her operation, and had no symptoms other than exertional dyspnea secondary to the essential hypertension which had recurred and remained at 260/120. X-ray of the chest showed no evidence of metastasis.

DISCUSSION

Although the patient had an elevated basal metabolic rate, definite clinical signs of hyperthyroidism were absent. The elevation of basal metabolic rate may have been due to a combination of (a) cardiac decompensation, (b) essential hypertension, and (c) vascular metastatic tumor.

Crile and McCullagh[9] have emphasized previously the importance of the aforementioned features as causes of an elevated basal metabolic rate.

This case is reported primarily to encourage surgeons to remove solitary metastases of tumors of low malignancy. Although 2 years* is too short a period of observation to enable us to speak of a cure, it is already apparent that the patient is much improved and that satisfactory palliation, if not a cure, has been effected.

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[9] Crile, G., Jr. and McCullagh, E. P.: M. Clin. North Amer., **24**: 395–409, 1940.

* To date approximately 3½ years have elapsed since operation.

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ECTOPIC URETER OPENING INTO A SEMINAL VESICLE

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Termination of the ureter in the seminal vesicle is a rare anomaly. Riba et al., including 1 instance of their own, reported 27 such instances. Subsequently Engel reported a single instance. Of the 28 instances, twenty-two were found at autopsy. In only six was a clinical diagnosis made and therapy applied. The present instance is the seventh* such to be reported.

CASE REPORT

R. F. H. (R-24614), a 28 year old, married white man was admitted to the Veterans Administration Hospital, Fort Howard, Maryland complaining of a painful "squeezing" sensation in his rectum for about 3 weeks. A vague discomfort had been present in the rectum for about 3 months. He had been treated for "prostatitis" without effect previous to admission. There had been no urinary or genital symptoms. His sexual life had been normal and he had fathered one daughter, aged three. The remainder of the history was noncontributory.

Physical examination was negative except for the rectal findings. The prostate was of normal size, shape and consistency. A soft, almost cystic, irregular, slightly tender mass bulged into the rectal lumen above the prostate. The right border of the mass was sharply defined and the lower border was continuous with the upper margin of the prostate, but the left border extended laterally and upward, higher than could be reached with the examining finger.

Routine examination of the blood and urine was normal. Cultural studies of the urine were negative. Roentgenograms of the chest and abdomen, barium studies of the colon, and cystogram were not unusual. Proctoscopy showed the mucosa over the mass to be freely movable and normal in appearance.

Excretory urography showed a normal right urinary tract, but there was no evidence of function on the left (fig. 1, *A*). Seminal vesiculography was done under local anesthesia by isolating the vasa in the scrotum, and injecting each vas in a retrograde manner with 15 cc of 35 per cent diodrast. Rectal palpation during this procedure demonstrated increasing distention of the mass previously described, giving presumptive evidence that the mass was seminal vesicle. Roentgenograms revealed a normal right seminal vesicle, and a tremendously dilated, coiled, left vesicle (fig. 1, *B*).

At cystoscopy, a moderate elevation of the trigone was found. The orifice of the right ureter was displaced upward and laterally but was easily catheterized.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* Since the preparation of this article, another instance has been published (Hamilton, G. R. and Peyton, A. B. J. Urol. **64:** 731-735, 1950). The present instance is therefore the eighth reported clinical case.

The left ureteral orifice could not be found and indigo carmine appeared only from the right ureteral orifice. The posterior urethra and verumontanum were normal.

The diagnostic possibilities seemed limited to 1) agenesis of the left kidney with accompanying left seminal vesiculitis, and 2) an atrophic left kidney with an ectopic ureter emptying into the left seminal vesicle. The latter diagnosis was considered more likely.

On April 13, 1950 an exploratory procedure was done through a left lumbar incision in the lateral position under spinal anesthesia. An almost completely atrophic kidney, measuring 5 by 2 by 0.4 cm., and consisting of a cap of fibrous tissue surrounding a small pelvis was found in the usual position. A hypoplastic renal artery about 3 mm. in diameter was present. The ureter, which proximally appeared fairly normal, became thickened and distended distally until it entered a tremendously enlarged, coiled, nodular and elongated seminal vesicle. The kidney and ureter were freed completely and placed in the lower portion of the wound which was then closed. The patient was turned to the supine position and a left lower pararectus incision of the lower abdominal wall was made. The kidney and ureter, freed from above, were exposed retroperitoneally and delivered into the wound. The ureter and seminal vesicle were followed retrovesically where a large, distended cyst, or diverticulum, of the seminal vesicle was found. Dissection was continued to the ejaculatory duct. At this point a needle was inserted in the ureter, 15 cc of dark brown fluid was aspirated, 35 per cent diodrast was injected and a roentgenogram taken (fig. 1, *C*). The vas deferens and ejaculatory duct were divided and the specimen removed intact. The course was uneventful and the patient was discharged on the twelfth day following operation. A sperm specimen obtained on the day of discharge was normal in every respect and contained 197 million sperm per cubic centimeter. At follow-up examination six months later, the patient was asymptomatic and had had normal sexual relationships.

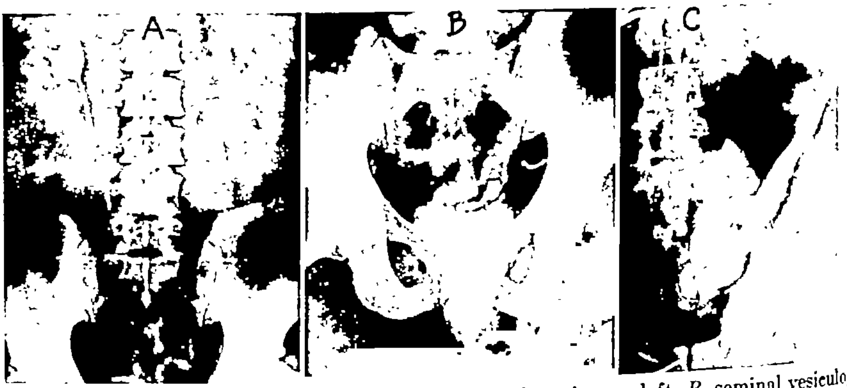

FIG. 1. *A*, excretory urogram showing absence of function on left. *B*, seminal vesiculography. Note enlarged left vesicle and faint outline of diverticulum. *C*, roentgenogram taken at operation after injecting ureter with diodrast. Note outlining of organs as compared to operative specimen.

The pathologist (Wm. B. VandeGrift, M.D.) reported that the kidney, measuring 5 by 2 by 0.5 cm., had a contracted pelvis. The ureter, approximately 15 cm. long and 1 cm. in diameter, opened into a dilated seminal vesicle about 15 cm. in length. A diverticulum, 8 cm. long and 2 cm. wide, with a thick wall was found at the lower margin of the seminal vesicle. The opening of the vas deferens was between the seminal vesicle and its diverticulum. See figure 2.

Microscopically, the tissue described grossly as kidney consisted of smooth muscle, nerves and fibrous tissue, containing occasional small and large tubules filled with debris and lined by deeply staining pseudostratified cells containing mucus. Glomeruli were not demonstrated. The epithelium of the ureter, semina vesicle, cyst of the vesicle and the vas deferens was of the pseudostratified columnar or transitional type. The submucosa was infiltrated with lymphocytes, plasma cells and eosinophiles with little evidence of fibrosis.

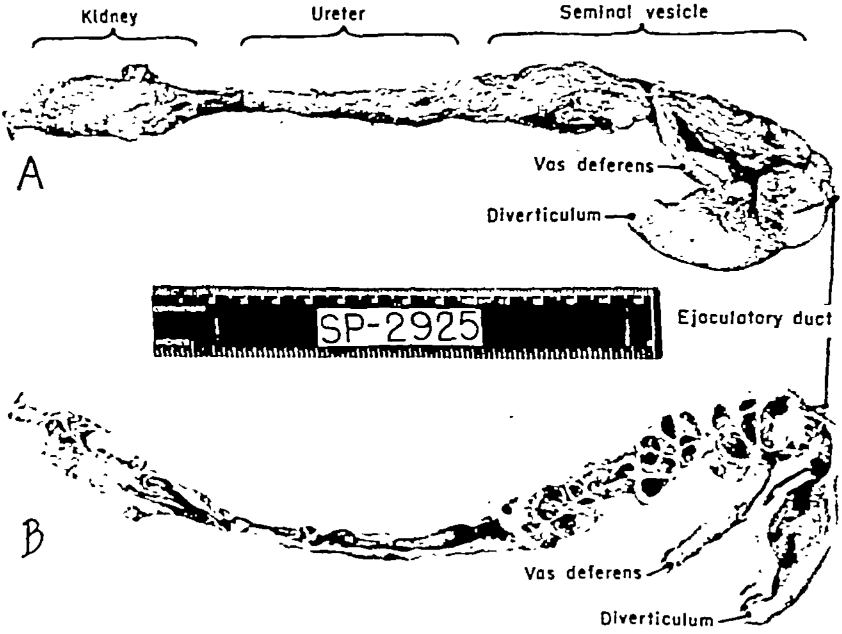

FIG. 2. *A*, Operative specimen, unopened. *B*, operative specimen, opened.

DISCUSSION

The ectopic opening of the ureter into the seminal vesicle is due to an anomalous development of the ureter. The lower end of the ureter, which develops by a budding process from the wolffian duct, normally is absorbed into the vesico-urethral anlage. The ureter becomes entirely separate from the wolffian duct which is the anlage of the male genital tract. When the ureter remains attached to the wolffian duct, the ureter may open into any of the derivatives of the duct. The openings of a series of ectopic ureters is listed by Thomas: prostatic urethra 33, seminal vesicle 17, vas deferens 6 and ejaculatory duct 5.

The present instance, in addition to the anomalous displacement of the ureteral orifice, exhibited the associated lesions of 1) hypertrophy and dilatation of the seminal vesicle, 2) diverticulum of the seminal vesicle and 3) hypoplastic, nonfunctioning kidney. As a cause of diverticula or cysts of the vesicle, Deming has postulated an antecedent stenosis of the ejaculatory duct which would seem to be a satisfactory explanation. The hypoplastic kidney found in this instance is commonly associated with ureteral ectopia, particularly of this type. Of 20 cases reported by McKirdie and Polkey, the kidney was absent in six, rudimentary in eleven and cystic in three.

Of the six previously reported cases, all but one had pyuria with associated urinary symptoms. This isolated instance of Engel was discovered during an investigation for sterility. The patient had a cavernous opening in the posterior urethra which proved to be a cystic seminal vesicle. Engel postulated regurgitation of semen into the vesicle as the cause of sterility. He stated that "a cystic seminal vesicle was removed and ureteronephrectomy performed," but how this was done was not described. Of the five other cases, in one, operation was not done, while in the others, multiple operations and prolonged treatment were required.

Our case differs from those previously reported in several particulars. Pyuria and urinary symptoms were absent. The presenting and only complaint was "squeezing in the rectum," a symptom previously unreported. Also unreported is the ballooning out of the seminal vesicle, as felt rectally, during vesiculography. We believe that this unusual clinical sign may be useful in evaluating the nature of masses in and around the prostate.

In our opinion, the diagnosis can be made clinically, if its possibility is kept in mind, and the following procedures done:

Excretory urography which will usually demonstrate a nonfunctioning kidney.

Cystoscopy which will show elevation of the trigone and absence of the ureteral orifice on the side of the nonfunctioning kidney.

Seminal vesiculography either by catheterizing the ejaculatory duct, or by injecting the vas in the scrotum, which will demonstrate an enlarged vesicle, a cystic dilatation of the vesicle, or a diverticulum, and may visualize the entrance of the ectopic ureter.

Rectal palpation which may reveal a mass at the site of a vesicle, and will demonstrate ballooning during vesiculography.

The indicated therapy is complete excision of the seminal vesicle and nephroureterectomy. It is conceivable that a functioning kidney may exist with such an anomaly, in which case the ureter might be transplanted into the bladder, and only the vesicle excised. There was no particular difficulty experienced in approaching the seminal vesicle from above and behind the bladder in this operation, and the use of this approach would seem to be justified by the possibility of saving an occasional functioning kidney.

SUMMARY

The seventh clinical case of an ectopic ureter opening into a seminal vesicle has been presented.

Associated lesions included a hypoplastic, nonfunctioning kidney, a large diverticulum of the seminal vesicle, and a stenosis of the ejaculatory duct.

Cure was effected by removal of the kidney, ureter and seminal vesicle in one stage.

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PRIMARY MEGALO-URETER

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Primary megalo-ureter as originally defined by Caulk[1] (1923) and as now generally accepted, is characterized by 1) a relaxed immobile ureteral orifice, 2) altered ureteral dynamics, 3) wide ureteral dilatation which is predominantly lateral with little or no ureteral lengthening, angulation or kinking, 4) free vesicoureteral reflux, and 5) occurring in the etiologic absence of obstruction, neuromuscular vesical disease or advanced (prolonged) infection. While the literature abounds with case reports allegedly of this condition, few of these citations stand critical analysis and in the writer's experience the condition as above defined is indeed a great rarity. Moreover, and at the risk of appearing a veritable urologic tyro, the writer has found among several hundred personally examined instances of dilated ureter(s) in infants and children only two cases in which the probable diagnosis of congenital ureteral atony seemed warranted. In many of the cases of advanced ureteral dilatation, the condition was associated with readily demonstrable neuromuscular vesical disease, while in others there was obstruction—either congenital or acquired—or prolonged infection explained the findings.

Etymologically megalo-ureter means enlargement of the caliber of the ureter, but other etiologically descriptive designations have been employed which sometimes confuse rather than clarify the definition; these terms include: congenital dilatation of the upper urinary tract, congenital atony of the ureter, primary atony of the ureter, and ureteromuscular dysplasia. Until the etiology in a given case has been precisely identified, it would seem best to use the term megalo-ureter.

ETIOLOGY

Hinman[2] has summarized the etiologic theories of megalo-ureter as follows: 1) persistence of the sausage type of fetal ureter, 2) obstruction by fetal valves which have subsequently undergone normal regression but have left a dilated ureter, 3) neuropathic dilatation, 4) inflammatory dilatation, 5) atonic dilatation (a) with, and (b) without an insufficiency of the ureterovesical orifice, 6) insufficiency of the ureterovesical valve, 7) spasmodic contraction of the bladder, 8) ureteral stasis due to toxins, and 9) pelvic dilatation as a result of spasm of the ureteropelvic junction—a form of congenital hydronephrosis. Chwalla's[3] theory of ureteral dilatation resulting from obstruction during fetal life and caused by a persistent vestigial membrane has been adduced to explain megalo-ureter. Yet the persistence of the disproportionately large fetal ureter may well

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Read at annual meeting, Northeastern Section, American Urological Association, Lake Placid, N. Y., September 21, 1951.

[1] Caulk, J. R.: The importance of the ureterovesical valve. J. Urol., 9: 315, 1923.

[2] Hinman, F.: Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935.

[3] Chwalla, R.: Process of formation of cystic dilatations of vesical end of ureter and of diverticula at the ureteral ostium. Urol. & Cut. Rev., 31: 499, 1927.

result from a faulty neuromuscular development as evidenced by atony and sometimes absence of peristalsis.

Dysplasia of the ureteral musculature has been advanced to explain megalo-ureter, it being noted that until the third or fourth month of fetal life, the ureters are unusually wide in comparison with the rest of the body. The fetal ureters are devoid of musculature until the second month when fibers begin to appear at the vesical end, and by the sixth month the entire ureter and pelvis have acquired their definitive musculature. According to the theory of dysplasia: 1) the mural development of the ureter may be incompleted, or 2) completed, the fibers are hypoplastic or the coating is unusually thin, or 3) the enormous ureteral dilatation of early fetal life simply fails to disappear. Retrograde pyelographic studies in infants three and four weeks old have commonly suggested congenital megalo-ureter but on examination two to four years later we have found the urograms normal.

The analogy has been drawn between the congenitally dilated ureter and the congenital megacolon of Hirschsprung (cf. infra), and similarly to congenital dilatation of the bile ducts as described by Kelsey.[4] Beer,[5] Braasch,[6] and others have adduced the explanation of inflammation rather than obstruction which has been countered with the argument that inflammation causes stricture rather than dilatation. Yet dilatation caused by chronic inflammation is a frequently observed urologic phenomenon and may well be an important secondary factor if not the primary cause in megalo-ureter. Heyman and Martin[7] recently reported a 20-month-old girl with urinary infection and extensive bilateral megalo-ureter (as well as megalo-bladder of which no point was made), presumably without demonstrable cause. The child was followed over a 6-year period during which time the only treatment (except possible dilation of the lower urinary tract coincident to one cystoscopic examination) was continuous chemotherapy for the infection. Yet during this time regression in the urinary tract dilatation occurred, the excretory urogram becoming essentially normal. The benefit was attributed by these authors solely to the sterilization of the urine, but I have seen several similar cases with similar evolution and do not consider them as true congenital primary megalo-ureter.

Until recently it has appeared that of the several potential causes of megalo-ureter as indicated in the third paragraph, theories 1 and 3 are the most reasonable to accept in the absence of obstruction. Yet, by the time the examination is made, an initial blockage may no longer be demonstrable. It is notable that wide dilatation of the ureters and pelves was recorded in twenty-three (unilateral 5; bilateral 18) of 15,919 autopsies in infants and children (ratio 1:692) in which no cause for the dilatation could be found.[8] But such observations are widely open to question and it seems unlikely that congenital dilatation alone explains the findings. It is recognized that prolonged overdistention of the ureter causes variable pressure anesthesia of the nerve endings and changes in the channel walls comparable to those occurring in the wall of the chronically overdistended bladder. Thus the ureteral reflex arc may be subdued or disrupted so that the stimulus for strong peristaltic contractions is ineffectual or lost. By this mechanism coupled with the increasing simple hydraulic pressure engendered by the fluid mass in the ureter, further dilatation is induced.

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[4] Kelsey, W. M.: Idiopathic dilatation of the common bile ducts in childhood. J. Pediat., 31: 211, 1947.

[5] Beer, E.: Neuromuscular vesical disease, sphincterospasm, in Beer and Hyman, Disease of the Urinary Tract in Children. New York: Hoeber & Co., 1929.
Chronic retention of urine in young boys due to bladder neck obstruction. J. A. M. A., 65: 1709, 1915; Ann. Surg., 79: 264, 1924.

[6] Braasch, W. F.: Stricture of the ureter. J. A. M. A., 91: 1263, 1928.

[7] Heyman, W. and Martin, J. F.: Bilateral megalo-ureter in a child. J. Pediat., 35: 618, 1949.

The first substantial and definitive studies of the cause of primary megalo-ureter have recently been made by Swenson and his coworkers.[9] These observations have been made tangential to their epochal discovery that the probable etiologic lesion in congenital megacolon (Hirschsprung's disease) is the congenital absence of parasympathetic ganglion cells (Auerbach's myenteric plexus) in the constricted nonperistaltic rectal or rectosigmoid bowel segment. Colonic peristaltic waves stop at the aganglionic segment; functional obstruction is produced at this point with massive dilatation and hypertrophy of the adjacent colon above. Resection of this aganglionic segment cures the disease with restoration of normal bowel function.

Rectum, rectosigmoid, and bladder are embryologically one (gut) with a common parasympathetic innervation through the pelvic nerves (nervi erigentes), one major branch of which goes to the lower bowel, the other branch to the bladder. In about a half of all cases of Hirschsprung's disease there is also vesical dysfunction which, though it may not cause recognized symptoms, is readily demonstrable by cystometry. The usual cystometric curve is that of a dilated atonic bladder with a low intracystic pressure until the viscus is well distended. Not infrequently in these cases there is associated megalo-ureter which is generally bilateral, an observation which has been made by several including Swenson et al. and the writer.

Reasoning that a common defect in the pelvic parasympathetic outgrowth from the primitive neural crest may give rise not only to an aganglionic segment of the colon but also to areas in the bladder in which development of the parasympathetic plexus is poor or absent, Swenson and his coworkers began histologic study of the bladder wall to determine if there is a decrease of parasympathetic ganglion cells as an etiologic factor in megalo-ureter. These studies[10] have con-

[8] Campbell, M.: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951.

[9] Swenson, O.: A new treatment for Hirschsprung's disease. Surgery, 28: 371, 1950.
—— and Bill, A. H., Jr.: Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon. An experimental study. Surgery, 24: 212, 1948.
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[10] Swenson, O.: *Personal communication.*
——, MacMahon, H. E., Jaques, W. E. and Campbell, J. S.: A new concept of the etiology of megalo-ureter. New England Med. Center Bull., August 13, 1951; New England J. of Med., in press.

clusively demonstrated a striking diminution of ganglion cells. By analogy, it seems likely that the same cycle of pathophysiologic function occurs in the ureter under these conditions as it does in the colon in Hirschsprung's disease, namely, ureteral peristalsis is maintained down to the aganglionic ureterovesical junction area with resulting relative adynamic obstruction (achalasia) and wide dilatation of the tract above.

In their studies of normal or control bladders, Swenson et al.[10] found an essentially uniform pattern of ganglion and nerve cell distribution, these cells being located chiefly in the vesical adventitia with greatest concentration in the areas adjacent to the entrance of the ureters into the bladder (lateral portions of the trigone) and in slightly lesser numbers around the seminal vesicles in the male and in the vaginal septum in the female. The number of nerve cells diminishes toward the midline, anteriorly and posteriorly, and toward the fundus and the urethra. The ganglion cells are of two types: 1) round, and 2) scalloped in outline. Yet satellite and neurolemma cells were found in great numbers, either singly or in large clusters, in the substance of the nerve bundles which, usually following the course of the larger vessels, pass from the adventitia to the deeper zone of the muscularis, and in lesser numbers to the superficial muscularis and submucosa. Nerve branches, predominantly nonmyelinated, were found in all layers of the bladders.

In contrast, histologic study of the bladder in patients with megacolon and vesical involvement and megalo-ureter showed a pronounced diminution of ganglion cells. This deficiency was so marked that, without identification of the source of the material and with the exception of one borderline case, several Boston pathologists could readily recognize and properly classify on the basis of the ganglion cell count, the tissue from the normal bladders and from the megalobladders and megalo-ureters. In short, the recognition of six out of 7 cases of megalobladder by nerve-cell estimation alone in a mixed collection of tissues from sixteen bladders, suggests that a diminution in parasympathetic nerve cells may be the anatomic basis for what has heretofor been considered a primary functional vesical disturbance. This study also suggests that the parasympathetic ganglion cells may not only be fewer in number but less well developed and functionally defective in these cases. Ganglion cells are found in small numbers in normal ureters and even in megalo-ureters.[10]

The faulty parasympathetic vesical innervation will be reflected in

1) poor detrusor function (incomplete bladder emptying, reduced frequency of urination and, as cystometrically demonstrated, diminished vesical emptying contractions and a slow gradual rise of intravesical pressure),

2) inadequate vesical neck opening (relaxation)[11] and, possibly,

3) diminished contraction of the ureter, the normal contracture of the lower end during urination being a mechanism calculated to prevent vesicoureteral reflux during this act.[12] Failure of this protective mechanism to operate

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[11] Barrington, F. J. F.: The component reflexes of micturition in the cat. Parts I and II. Brain 54: 177, 1931.

[12] Kuntz, A.: The Autonomic Nervous System. Philadelphia: Lea and Febiger, 1947.

might be expected in parasympathetic dysfunction consequent to abnormal neurogenesis; vesico-ureteral reflux almost always exists in megalo-ureter.

Because of the subnormal parasympathetic nerve function, the bladder is unable to empty itself with consequent increasing residuum and intracystic pressure, the latter commonly mounting to 30 or 35 cm. of water pressure, and affording an augmented hydrostatic force against which the kidneys must excrete and ureteral peristalsis propel. The natural end result of this is megalobladder, dilated ureter(s) and hydronephrosis. These deleterious forces coupled with the increased abdominal pressure called into play to initiate voiding, induces ever greater vesical and ureteral dilatation. Parenthetically, it is in this group of cases of neuromuscular vesical disease that limited transurethral resection of the bladder neck is often therapeutically effective even though the cysto-urethroscopic study discloses no apparent obstruction.

In most instances of extensive ureteral dilatation consequent to neuromuscular disease, the localized etiologic factors, the pathologic anatomy, and the clinical and therapeutic problems are primarily concerned with the more comprehensive picture of neuromuscular vesical disease. This observation explains not only why isolated ureteromegaly is such a rare condition but indicates the diagnostic nonacceptability of scores of cases reported in the literature as primary megaloureter. In many there was urographic evidence of neuromuscular vesical disease while the examination in other cases disclosed obstruction at the vesical neck or peripherally, most often identified as contracted bladder neck but which well may have been neurospastic in character. In short, it is the writer's belief that megalo-ureter must always be considered a collateral manifestation in neuromuscular vesical disease rather than an isolated lesion and not to be confused with those cases of excessive ureteral dilatation consequent to nonneurogenous obstruction or other disease.

SYMPTOMS

Megalo-ureter may provoke no symptoms, but in many cases there is persistent pyuria, urinary frequency, hematuria, pain in the loin and/or bladder, and present singly or in combination. As total renal back-pressure injury progresses, the systemic symptoms of urinary toxemia and renal failure are noted.

DIAGNOSIS

The diagnosis is made by urologic examination demanded by the presence of any or all of the symptoms indicated in the preceding paragraph. An initial excretory urographic study may suggest the diagnosis but the mere demonstration of greatly dilated ureters alone is not enough. Cystography discloses massive ureteral reflux while cystoscopy and ureteral instrumentation fail to reveal obstruction. Estimation of the residual urine in these cases may be misleading unless it is done at once after voiding, for the urine from the greatly dilated upper tract reservoirs will promptly drain down to fill the bladder partially and give an untrue estimation. By cystography, cystoscopy, ureteral chromomeatoscopy and retrograde pyelography, if necessary, the features of megalo-ureter as defined in the first paragraph will be identified. The presence of neuromuscular vesical disease should be readily confirmed by cystometry. It is notable that the ureterovesicial junction is not strictured or even tight in primary megalo-ureter and that large ureteral dilating instruments can readily be passed into the ureter even though the urographic conformation of the intramural ureterovesical junction appears normal.

TREATMENT

Rational therapy in primary megalo-ureter will be guided by precise diagnosis as well as clinical considerations such as the general condition of the patient, complicating lesions and obstructions and, of utmost importance, the degree of renal damage and infection. The last are determining factors in the prognosis.

In unilateral megalo-ureter with hopeless renal damage and infection, employ ureteronephrectomy with removal of the ureter down to the bladder wall.

The use of parasympathomimetic drugs (mecholyl, acetylcholine, doryl, urocholine, transentine, etc.) has been without appreciable benefit in the treatment of primary megalo-ureter.

In Hirschsprung's disease and before rectosigmoid excision was employed, prompt regression of the colonic dilatation and return to normal caliber regularly followed colostomy drainage. In bilateral primary megalo-ureter, decompression of the distended duct by suprapubic cystostomy drainage has brought about the most satisfactory anatomic and functional improvement with regression of the dilatation and, albeit a temporizing measure, it is to my belief, the only procedure to accomplish this result with any regularity.

These children, equipped with a flounder bag type of urine collector, manage well and with remarkable convenience, frequently becoming capable of attending to their own apparatus and even changing the suprapubic tube. Free bladder drainage is maintained for four to six months or longer, until such time as the urologic investigation and notably the urographic findings, show a satisfactory regression of upper tract dilatation. When this is achieved, the cystostomy drainage is discontinued. Four or five times a day at regular intervals the child is made to empty his bladder, employing low abdominal manual compression if necessary in order to reduce the residuum to as near zero as possible. Chemotherapy is simultaneously administered as necessary to maintain urinary sterilization. Under this regimen, the improvement will often be maintained but in some cases regression to the former unfavorable status occurs and again demands cystotomy bladder drainage or perchance in some cases, transurethral bladder with resection.

Resection of the lower end of the ureter with ureteroneocystostomy has been successful in some cases (Parke Smith[15]), perhaps because the ureterovesical junction is transferred from a bladder wall segment in which parasympathetic ganglion cell development is subnormal or meager. This is the only explanation which appears logical under the circumstances and in view of newer knowledge.

Excision of a wide longitudinal strip the length of the ureter with suture closure

Smith, Parke. Personal communication.

of the duct to reduce its lumen has been employed without striking success. Yet, coincident with this operation and the establishment of temporary cystostomy drainage, marked improvement with disappearance of the extreme dilatation has been observed in the megalo-ureter mate not operated upon (Nesbit;[14] Kimbrough[15]).

In secondary megalo-ureter the treatment is eradication of the neurogenic or other obstruction and/or infection and in many of these cases simple transurethral bladder neck resection produces gratifying results in the absence of uretero-vesical junction blockage. The last demands appropriate treatment by wide ureteral meatotomy, ureteroneocystostomy or, as we have frequently and satisfactorily used, a ureteral pull-through procedure to establish an orifice of wide patency and at the same time excise much of the redundant ureter.

SUMMARY

Primary megalo-ureter is a rare disease. Most alleged cases of primary megalo-ureter are in truth secondary megalo-ureter associated with neuromuscular vesical disease which is unrecognized or its etiologic relation to the advanced ureteral dilatation passes unheeded. The older theories of its etiology have been briefly discussed. The probable etiology has recently been identified by Swenson and his coworkers who have demonstrated a striking reduction in parasympathetic ganglion cells in the bladder wall musculature surrounding the ureteral orifices, a finding similar to their discovery of the absence of these cells (Auerbach's myenteric plexus) in the rectum and rectosigmoid in Hirschsprung's disease, and in half of the cases of which there is associated neuromuscular vesical disease and in a lesser number, megalo-ureter. The symptoms and diagnosis have been indicated. Neuro-urologic study including cystometry is essential. The various therapies which have been employed in these cases in the past and their shortcomings have been cited. Only the establishment of free cystostomy drainage has been regularly effective in bringing about the regression of the ureteral dilatation, in some cases even to restoration of normal ureteral and pelvic caliber.

140 E. 54 St., New York, N. Y.

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[15] Kimbrough, J. C.: Personal communication.

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CARCINOMA OF THE URETER

ALBERT A. CREECY

Despite the fact that since March 1948, sixteen papers relating to carcinoma of the ureter have been published in the *Journal of Urology*, additional data on this rare lesion seem warranted. W. W. Scott, Long and O'Conor have emphasized the need for more information as regards treatment and results. Renner found 3 ureteral tumors in 13,854 autopsies; Jaffe and Mendillo reported only 2 cases in 90,000 routine hospital admissions; and Colston listed 2 cases of primary carcinoma of the ureter in a total of 22,000 urological cases. Long in 1948 brought the number of cases reported up to 201, since which time at least 15 additional cases have been added bringing the present number to 216.

The group to be cited here consists of 7 cases of primary carcinoma of the ureter and 1 case of metastatic carcinoma of the ureter from a lesion in the prostate gland. The first patient in the group was seen in 1931 and the remaining seven have been seen since 1947. This is in comparative ratio with the fact that two-thirds of the cases of carcinoma of the ureter have been reported in the last decade and tempts one to wonder if the increase is entirely due to better diagnostic acumen, increasing longevity or possibly an increased exposure to exogenous carcinogens, as was hazarded by Davis in 1943. According to Hamm and LaValle, ureteral tumors occur most frequently in the sixth and seventh decade and the average age is 55 years. They predominate in men in the ratio of two to one and the right ureter is involved more frequently than the left with 75 per cent of the lesions appearing in the lower third. In this series of 8 cases six occurred in men and two in women; 6 cases were in the eighth decade, one in the seventh and one in the sixth. Hematuria, pain and a mass in the flank or back were the most common symptoms occurring numerically in the order mentioned with the first two being present in almost all cases. Diagnosis is made from the history, physical examination, laboratory findings, cystoscopy, and pyelogram. At cystoscopy blood may be seen emerging from the orifice on the affected side and if a papillary projection is present, then the correct diagnosis is almost assured. Obstruction to the passage of a catheter in the very lowest part of the ureter may be encountered and if on injection of opaque medium under some pressure a film is obtained showing irregular dissemination then a tumor mass may be suspected. Vaginal examination in women and rectal examination in men will also be of value in diagnosing lesions in the terminal ureter. If the catheter meets a soft or mushy obstruction higher up this may help differentiate tumor from stone. A pyelo-ureterogram is most helpful giving the characteristic goblet-shaped obstruction or ring shadow, as Crance calls it, and hydro-ureter and hydronephrosis above with diminution in function. The most disturbing differential diagnosis to make is that of a small or nonopaque calculus, and in view of the radical surgery required for tumor of the ureter an error

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in this regard would be most distressing. Use of the wax bulb and study of smears by experienced pathologists using the Papanicolaou method should be of diagnostic aid.

Ureteral tumors tend to multiplicity and recurrence, and these facts have stimulated many authors to advance explanations for this behavior. Von Brunn's description of the downward proliferation of the basal epithelial layer to form cell buds and nests has led Bothe to think that some carcinogen activating these areas may account for these characteristics. On the other hand, Fagerstrom questions Von Brunn's theory as to the mechanism of the formation of cell nests believing that they are abnormal patterns resulting from hyperplasia of the epithelium which in turn may be due to local irritation such as chronic infection or from noxious agents circulating in the body fluids. Gualtieri, Hayes and Segal accept Von Brunn's cell nests as the basic nuclei from which ureteral lesions develop and believe that it substantiates Ewing's hypothesis of the multicentric origin of these tumors. They believe that in addition to an abnormal urothelium, sensitization by general and local factors, a catalyst carcinogen, lytic enzyme action, numerous chemicobiological actions, growth directions and epithelial changes are also contributing factors in the developing of ureteral tumors. Kirwin believes an infectious agent in the form of a filterable virus may be the activating cause. Recurrence by lymphatic extension and by direct implantation must be recognized as potential factors. The presence of a carcinogen in the activation of ureteral lesions is accepted by many, and its most likely source would seem to be in the excretory product of the kidney. If this be true two facts remain to be explained: One is that the condition is usually unilateral indicating that only one kidney is excreting carcinogen; the other is that even after removal of a kidney with a large portion of ureter, tumor formation will recur in the stump. W. W. Scott, in reporting a case of recurring bladder papillomatosis arrested by nephro-ureterectomy and partial cystectomy for carcinoma of the ureter, offers as an explanation the possibility of a unilateral excretion of carcinogenic agent from one kidney due to alteration of the filtration threshold from some general systemic force or functional change.

Once the diagnosis is made it seems generally agreed that the best treatment is complete nephro-ureterectomy removing a cuff of the bladder wall in a one stage operation. If the bladder wall around the orifice is not removed it should be desiccated after the method of Colston. If the patient's condition does not permit doing the operation in one stage, then the tumor-bearing portion should be removed first and the second part done as soon thereafter as possible. This adds increased possibility of recurrence as the stump of the ureter harbors a restless urothelium with chronic inflammation and lymphocytic infiltration which can become malignant and spread rapidly. The subject of benign tumors poses a difficult problem in diagnosis and treatment. A fortunate trend in urology has been conservation of renal tissue but when applied in lesions of the ureter it is attended with considerable hazard. Vest has presented a very valuable study in this regard on seventy odd cases of benign tumor of the ureter citing three of his own in which he elected to do conservative surgery. He states that treatment of ureteral tumors should be governed by the type of tumor with which one is dealing and this of course usually requires biopsy. His position has been questioned, but not justly so because he takes great care in stating his criteria for selecting cases, and if these are followed one can hardly make a mistake. Furthermore, he has emphasized that carcinoma of the ureter is a deadly serious disease and one in which early diagnosis with radical removal of the kidney, ureter and a portion of the bladder offers the only hope of cure and that it would be fatal to err on the side of conservatism when dealing with cases of questionable malignancy. In the cases he treated conservatively good function on the affected side was necessary, biopsy showed benign tumor and in all 3 cases reported there was impairment of total renal function and definite necessity for renal salvage. Edelstein and Marcus have also advocated conservative surgery in dealing with connective tissue tumors such as lipomas, fibromas, myomas, but in their report of 1 case which they state was a benign papilloma of the ureter they wisely elected to do nephro-ureterectomy and the patient was alive and well 15 months after surgery.

A majority of tumors of the ureter are highly malignant and there is a growing trend to regard and classify the benign papilloma as an early papillary carcinoma. Because of its multiplicity, frequency of recurrence and tendency to malignant degeneration, some urologists and pathologists believe that a benign papilloma of the ureter is as rare as a benign skunk. The prognosis for survival over 2 years is poor according to Burford, Glenn and Burford. One reason for this is anatomical, due to the thin wall and rich blood and lymphatic supply of the ureter which favors early metastasis. Lowsley and Kirwin state that even in favorable cases the outlook is bad. Counseller, Cook and Seefeld reported 18 cases and of six treated by complete nephro-ureterectomy, four were dead within 3 years. The postoperative mortality is high being 24 per cent according to Stang and Hertzog, and about 25 per cent according to Long. One of the most encouraging reports is that of O'Conor who did complete nephro-ureterectomy in 8 cases and had six alive at 11, 9, 8, 7, 5, and 2 years after operation. Another lived 10 years dying of a stroke and in the eighth case the patient died 3 years after operation of metastasis. The follow-up of cases along this line is constructive and answers a plea first made by W. W. Scott and later by Long for this type of report.

CASE REPORTS

Case 1. J. S. R., a white man, aged 71 years, was first seen in December 1931, with a history of hematuria of 2 weeks' duration without pain or frequency. Physical examination was negative except for early benign hypertrophy of the prostate. The urine was grossly bloody. Cystoscopy revealed no evidence of tumor in the bladder, and both ureteral meati appeared normal although a catheter could be introduced a short distance up the right side. A catheter passed normally to the left renal pelvis; the pyelogram on that side was normal whereas medium injected into the right catheter showed no dye in the right urinary tract but a diffuse irregular distribution of dye in the lower right ureter flowing back into the bladder. Excretory urography showed a normal left kidney. Thirty minutes after injection the right kidney pelvis and calyces were markedly dilated but the right ureter did not fill. The conclusion was that the case was one of benign hypertrophy of the prostate, and a tumor of the right ureter. Operation was refused.

The patient returned May 1933, complaining of recurring attacks of right renal pain. He had passed very little blood until the last 2 weeks. Physical examination showed a well preserved man of 73 years of age. The lungs and heart were normal. The blood pressure was 155/80. No enlargement of liver or kidneys was present. Early hypertrophy of the prostate was noted. On rectal examination a hard, fixed tender mass was felt on the right side above the prostate. The blood count showed no anemia and the nonprotein nitrogen was normal. Again at cystoscopy the left kidney was normal but the right ureter was obstructed just above the orifice. A diagnosis of right hydronephrosis, due to tumor of the ureter was made and nephro-ureterectomy recommended. The right kidney and ureter were removed but the terminal ureter was fixed, the tumor mass invading the surrounding structures and could not be removed. The patient made a smooth recovery and the gross hematuria subsided. He was discharged in May 1933, and progressively went downhill dying of metastatic carcinoma August 1933, about 18 months after the first admission. Autopsy showed metastases to the liver, retroperitoneal lymph nodes and to the urinary bladder. The right ureter was absent to a point 4 cm. above the brim of the pelvis. It passed into a large tumor mass that measured 12 cm. in diameter. When the tumor mass was removed erosion of the ilium, sacrum and the last lumbar vertebra was noted and the common iliac artery was completely surrounded.

Study of sections of the tumor showed it to be made up of atypical epithelial cells which appeared to be transitional squamous cell in type, as occurs in the ureter. They varied in size and shape and showed many mitotic figures (fig. 1).

Case 2.—The case of Mrs. B. M. aged 70 years is reported next because of some similarity to the preceding case. She was referred by Dr. W. J. Sturgis, Jr. January 11, 1950, and complained of pain in the left flank. She had also noticed blood in her urine but this was not profuse. She had some dysuria and frequency. On physical examination no masses could be palpated, although on pelvic examination some induration and tenderness were noted in the region of the left ureter. Cystoscopy disclosed that the bladder mucosa was normal. Emerging from the left ureteral orifice was a small blood clot forming a cast of the ureter. Catheters passed into the left ureteral orifice were obstructed at 2 cm. A Woodruff bulb catheter was then introduced and skiodan injected with some pressure. The dye did not enter the upper ureter but returned into the bladder and extravasated into an irregular mass in the lower ureter. Previous excretory urography and cystoscopy showed good function and a normal right kidney. A diagnosis of carcinoma of the left ureter was made and the patient was returned to Dr. W. J. Sturgis, Jr. who did a complete nephro-ureterectomy (fig. 2). Microscopic sections revealed a highly malignant, grade 4 transitional cell carcinoma of the ureter which tended to be invasive in character. (fig. 3).

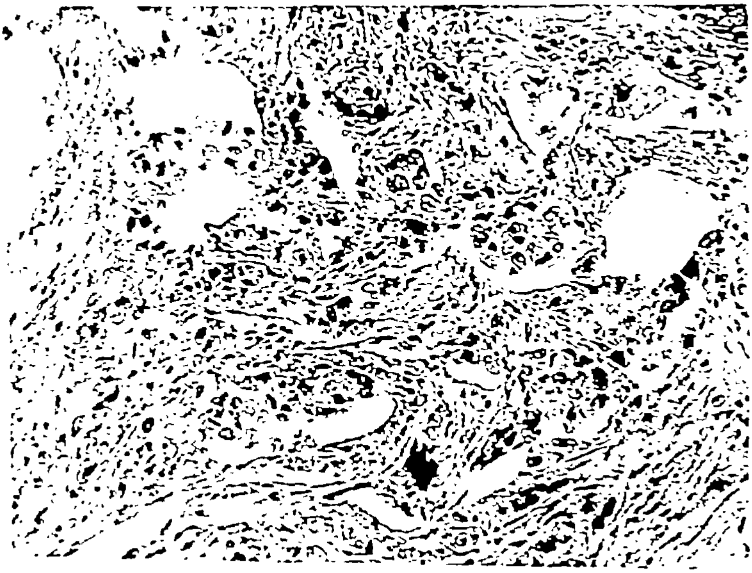

FIG. 1

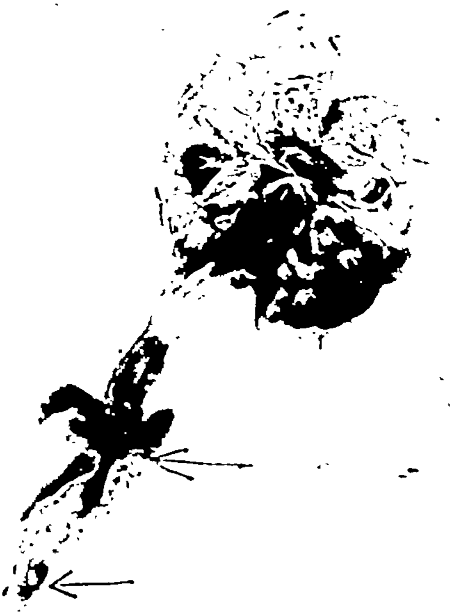

FIG. 2

In spite of this the patient has made a good recovery and is in good health 16 months after operation.

Both of these patients had carcinoma of the extreme lower ureter with similar symptoms and cystoscopic findings. One was seen in 1931, the other in 1950. The prompt diagnosis and the patient's acceptance of early surgical intervention in the second case has resulted in alleviation of pain and bleeding and with a reasonable hope of increasing her life expectancy.

Case 3.—Mrs. E. H., aged 51 years, was admitted to the hospital September 18, 1949, with pain in the left flank and abdomen of 5 days' duration. She was treated at home by her family physician who gave opiates for relief and then sent her to the hospital. She had had some dysuria and frequency with hematuria once, but on admission to the hospital urinalysis was negative for blood and pus. Physical examination revealed a hypertension of 220/110 with a systolic murmur over the entire precordium. The abdomen was obese. She had pain on pressure over the left lower quadrant. No enlargement of either kidney was detected. On cystoscopy, the right ureter and kidney were entirely normal, but an obstruction was met in the left ureter at 15 cm. which could not be passed. Injection of dye through the catheter revealed a block in the left ureter giving a goblet shaped appearance with no dye in the pelvis. Excretory urography revealed good concentration with normal pelvis on the right side. There was marked hydronephrosis on the left but the ureter did not fill. A diagnosis of tumor of the ureter was made. At operation 5 days after admission the left kidney was exposed and the ureter traced down to the pelvic brim where a nodule was palpated. The ureter was mobilized well below this point, clamped and ligated. The kidney and ureter were removed in the usual manner. On opening the ureter after removal the tumor was sessile in appearance, seemed

FIG. 3

to be well circumscribed, and measured ½ cm. in diameter. The distal portion was not removed (fig. 4).

The gross specimen consisted of a kidney 11 cm. from pole to pole. The pelvis and calyces were dilated. The attached ureter measured 14 cm. in length. A tumor mass was seen at the lower end which was whitish in color and firm in consistency. The ureter above was dilated and the ureter below was normal.

Sections of the tumor mass showed it to be made of atypical cells of the transitional squamous type which varied in size and shape with many mitotic figures noted. The ureter above and below showed a marked infiltration of lymphocytes. Diagnosis: squamous cell carcinoma of the ureter. (According to Melicow, infiltrating malignancies may present a squamous cell metaplasia.)

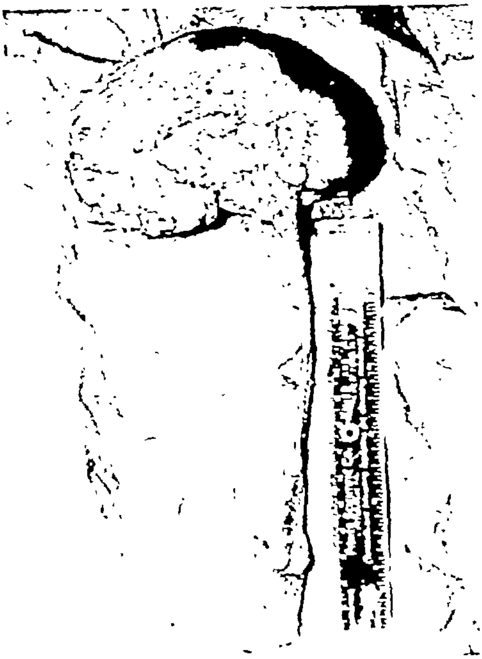

FIG. 4

The patient made an uneventful recovery and was discharged. Five months later she returned complaining of pain in the incision, left lower abdomen and radiating down the left thigh to the knee. She had lost weight. The blood pressure was 150/100. The abdomen was still obese but a mass could be palpated in the left midquadrant which was quite tender. Urinalysis was negative and there was no evidence of metastasis in the lungs or osseous system. X-ray therapy was given and the mass regressed slightly but the patient's general appearance was one of beginning cachexia. She returned 6 weeks later obviously much weaker with the mass increasing in size. She died at home 8 months after the initial onset of symptoms.

In this case the diagnosis was made early, treatment instituted promptly, and the lesion was quite small. However, it is believed that if a complete nephro-ureterectomy had been performed, the patient would have had a better chance for cure. This is particularly emphasized by the fact that recurrences are usually found in the remaining stump of the ureter or in the adjacent bladder tissue if not removed or desiccated, and as O'Conor has emphasized, these secondary lesions are often more extensive than the primary one. They also seem to develop a more malignant potential, invading adjacent tissues as though they were ideal culture media. Indeed, Bunge and Stein have found that transitional cell carcinoma of the ureter is a most favorable tumor to grow in vitro; they are studying the biochemical dynamics of tumor growth in the belief that respiratory studies, the use of various hormones in the medium, the assimilation of radio isotopes and use of folic acid antagonists offer new possibilities in experimental work on cancer. Research in this field is most welcome and may add to our knowledge facts which will help support or disprove the studies on pathogenesis and etiology which have been so ably advanced by Bothe, Fagerstrom, Gualtieri, Hayes, Segal and Kirwin. This case is a good example of the necessity for doing a complete nephro-ureterectomy and an argument against conservative surgery, especially opening the ureter and taking a biopsy, as it is almost impossible to do so without danger of spilling or implanting some of these highly malignant cells before operation is completed.

Case 4.—Mr. R. T. W., aged 70 years, was admitted to the hospital March 7, 1950. The case is reported through the courtesy of Dr. W. J. Sturgis, Jr. One sister had died of carcinoma of the ureter. Two and a half years prior to admission the patient first had bloody urine unaccompanied by any other symptoms. Six weeks previous to admission a pain developed in the small of the back and 2 days later the patient noticed murky urine. The hematuria had apparently always been relieved by medicine given by his family physician. On physical examination the patient was a well preserved white man. The blood pressure was 190/100. The cardiac rhythm was abnormal with extrasystoles. The prostate was enlarged about 2 plus, but was neither hard nor nodular. Excretory urography revealed a nonfunctioning left kidney and a normal upper right urinary tract. Retrograde pyelography showed dilated minor calyces at the upper pole of the left kidney and a bulbous lower half left kidney with no calyx extending into it. At operation on March 15 a complete nephro-ureterectomy was done. The postoperative course was gradually downhill characterized primarily by abdominal distention which persisted despite efforts to decompress the gastro-intestinal tract by intubation. The nonprotein nitrogen was 88.8 three days prior to death, which occurred 11 days after operation. Examination of the specimen revealed a tumor at the ureteropelvic junction.

Microscopic study of the sections disclosed carcinoma and showed much the same architecture as papilloma of the ureter with malignant changes. Final diagnosis: Papillary carcinoma, ureter, left.

Case 5.—Mr. T. L., aged 70 years, was admitted to the hospital in May 1948, complaining of blood in the urine. The present episode started 1 week prior to admission. He had no pain. He had frequency about 4 times each night. He gave a history of hematuria 1 year previously. This disappeared following treatment by his family physician only to recur 6 months later. On physical examination patches of psoriasis were seen on his knees and elbows. Excretory urography showed that the left kidney was normal in function, drainage, and appearance. The right kidney function was impaired. On cystoscopic examination an obstruction was met in the right ureter at 9 cm. Retrograde pyelogram showed an irregular filling in the midportion of the right ureter suggestive of a space-taking lesion. Dilatation of the proximal ureter and marked hydronephrosis of the right kidney were present. Urinalysis showed 2 plus albumin and 6 to 8 red blood cells. The nonprotein nitrogen was 65 before operation, and 67 on the day of death. The blood pressure was 220/110. Nephro-ureterectomy was done on June 3, 1948. The immediate postoperative result was good. The patient was allowed out of bed, but on the second postoperative day lapsed into coma and died suddenly. A necropsy was done. Examination of the surgical specimen revealed the upper 16 cm. of the ureter greatly distended. There was a firm, bulbous swelling in the distal 4 cm. On opening the ureter the upper portion was about 3 cm. in circumference. The swelling was due to multiple, soft, white polypoid masses with a broad, sessile, infiltrating base extending for about 4 cm. up the ureter. A projecting tongue extended down to a point of constriction. Section of the ureter revealed that the tumor extended into and infiltrated the mucosa. Microscopic section of the ureter adjacent to the tumor showed tremendous heaping of the transitional epithelium and as one approached the tumor it became definitely papillary in type but was composed of closely packed papillae. There was, however, no invasion of the muscularis. The stroma was scant and mitoses were rare. Perivascular round cell infiltration was also manifest in the surrounding fat. Diagnosis: Papillary carcinoma ureter, grade 2.

Case 6.—Mr. S. M., aged 64 years, was admitted to the hospital April 28, 1949 with a chief complaint of backache. He had had backache for several weeks and was unable to work. He had lost weight. No hematuria was present, but he had some frequency. Physical examination showed loss of weight. Bronchial rales were present throughout the chest. The heart was slightly enlarged to the left. The prostate was slightly enlarged and indurated. The blood pressure was 130/76. Cystoscopy revealed a small papilloma on the right lateral wall of the bladder just above the meatus. A catheter passed easily to the right kidney pelvis, but an obstruction was met in the midureter on the left. A retrograde pyelogram revealed a normal pelvis on the right but pyelogram of the left kidney showed hydronephrosis with a filling defect in the middle third of the left ureter.

A papilloma of the bladder was destroyed by fulguration. Biopsy of the tumor revealed papillary fragments with little stroma and quite cellular. Few mitotic figures were seen. One week later a left nephro-ureterectomy was done. Pathological examination of the surgical specimen showed that the pelvis and calyces were distended and filled with thick purulent material. On opening the ureter the lower 3 cm. was occupied by a sessile tumor mass which had some papillary arrangement. Microscopic study showed a papillary tumor in the ureter with anaplastic cells containing large irregular nuclei, mitoses, cell atypism and marked invasion of the lymphatics in the wall of the ureter. Tumor tissue was even found in the adherent blood clot. Final diagnosis: Ureter, papillary carcinoma, grade 4. Prompt recurrence was to be anticipated.

Four months after operation the patient died and autopsy showed metastases to the liver.

Case 7.—Mr. W. L. T. was admitted to the hospital July 27, 1948 complaining of weakness in the left arm and left leg. A jacksonian type of epilepsy developed followed by confusion and headaches. It was believed that this patient had a brain tumor, but an operation was not performed due to his advanced age and poor condition. He gradually became comatose and died quietly 1 month after admission. Laboratory examination revealed a few red blood cells, granular casts and many pus cells in urinalyses while he was in the hospital. Necropsy revealed a squamous cell carcinoma of the lung with metastasis to the brain. An incidental finding at the post-mortem examination was a small papillary carcinoma of the right ureter. It was located at the distal third of the right ureter and measured approximately 1½ by 1 cm. in diameter. Grossly, it appeared to have originated from the mucosa of the ureter. However, there was no obstruction or dilatation of the ureter proximal to this tumor. Microscopic examination showed atypical delicate papillary structure with a scant stroma, a narrow pedicle and no invasion of the stroma. No urograms were taken on this patient.

Case 8.—E. C. K., aged 73 years, a white man, was admitted to the hospital on May 19, 1949 complaining of pain in the right kidney. He had suffered constant pain 1 week prior to admission. Had passed no stones or blood. Pain radiated across the lower abdomen. He had had nocturia 2 to 5 times for 3 years. On examination the blood pressure was 160/114. The patient had tenderness in the upper portion of the right ureter. The prostate gland was hard, fixed and nodular. An excretory urogram was unsatisfactory. A retrograde pyelogram showed the left ureter and kidney to be normal. On the right there was a moderate degree of calyectesis and hydronephrosis. There was moderate dilatation of the proximal two-thirds of the right ureter with marked narrowing at the junction of the middle and distal thirds. It was thought that the patient had a stricture of the ureter with hydronephrosis of the right kidney. Gallbladder studies revealed cholecystitis and cholelithiasis. An x-ray revealed osteosclerosis of the bone in the region of the acetabulum and superior ramus in the pubis on the left. Similar changes were present in the ilium just above the acetabulum as well as in the left lumbosacral articulation. These changes were compatible with metastatic prostatic carcinoma. Laboratory findings: nonprotein nitrogen 27, serum acid phosphatase 6.2 units, cephalin flocculation 2 plus. Because of intractable renal colic, a right nephro-ureterectomy was done. Convalescence was uneventful. The patient was placed on stilbestrol 5 mg. daily. The surgical specimen consisted of a kidney 11 by 6 by 4 cm. with 12 cm. of ureter attached. The pelvis and ureter were slightly dilated. The distal end of the ureter showed some thickening of the wall and the lumen was narrowed at this point. Sections of the ureter showed infiltration of the surrounding tissue particularly the perivascular lymphatics with glandular tissue composed of small tubules with pale cuboidal cells resembling prostatic cells. There was no mitosis and very little cell atypism. The nuclei were large, vesicular and had a prominent nucleolus. The ureteral mucosa was intact in the specimen removed. Impression: Metastatic carcinoma of the ureter suggestive of primary carcinoma of the prostate. The patient was living 23 months after operation. He was still on stilbestrol therapy.

True, metastatic carcinoma of the ureter is rare. Thirty-five cases were collected by Presman and Ehrlich in March 1948, to which they added 2 cases of their own. By true metastatic carcinoma is meant carcinoma that invades the ureter by the lymphatics and blood vessels from a lesion elsewhere in the body and has not invaded by direct extension from a lesion such as carcinoma of the renal pelvis or bladder. In one of the cases reported by Presman and Ehrlich, the primary lesion was in the lung and the other was in the stomach. Of the 37 cases reported, eight were from the prostate, eight from the stomach, four from generalized lymphoma, three from the cervix and two each from the bladder, breast, lung, colon, and ovary. Lazarus states that the criteria for true metastases to the ureter are the establishment of a primary lesion elsewhere, the cells in the primary lesion and the metastatic lesion must be similar and that these cells can be demonstrated microscopically in the perivascular lymphatics or blood vessels of the ureteral wall. In 1941, he reported 18 cases, seven of which originated in the prostate. It would seem that the case cited here is a true metastatic carcinoma of the ureter originating in the prostate, based on the clinical laboratory and x-ray findings in conjunction with the pathological description of cells resembling prostatic carcinoma invading the perivascular lymphatics.

SUMMARY

Eight additional cases of carcinoma of the ureter have been reported. Seven of these were primary carcinoma of the ureter, one of which was found at autopsy. The remaining case was metastatic from the prostate gland. Six of the cases of primary carcinoma came to operation, partial nephro-ureterectomy being done in three, all of whom died within 1 year. Three patients all 70 years of age or over had complete nephro-ureterectomy: one was alive and well 16 months after operation and 2 died postoperatively within 48 hours. The patient who had metastatic carcinoma from the prostate underwent partial nephro-ureterectomy and was alive 2 years after operation.

From these facts it is evident that carcinoma of the ureter is being seen more commonly than in the past, that it is a very fatal disease and that the best hope for cure is complete nephro-ureterectomy despite the fact that the mortality rate, especially in the aged, is still high.

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SPONTANEOUS RUPTURE OF THE URINARY BLADDER IN A MALE

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We are herewith reporting a recently encountered case of an interesting and unusual type of rupture of a hollow viscus. The experienced urologist, or surgeon, has, from time to time encountered a case of rupture of the urinary bladder. Such rupture almost always is secondary to trauma in the nature of external violence, instrumentation (transurethral resection), or to some predisposing pathologic condition within or adjacent to the bladder, the bladder outlet, or the urethra. In the female certain conditions associated with pregnancy at term, such as labor or manual expression of the placenta, have been responsible for rupture of the urinary bladder. In the male, attempted micturition during acute retention due to organic vesical neck obstruction has, in rare instances, resulted in rupture of the urinary bladder. Intrinsic specific infectious disease such as tuberculosis, has been reported as causing bladder rupture. Finally, in the presence of neurogenic dysfunction secondary to vertebral or intraspinal disease, the urinary bladder has been known to rupture.

Stone[1] reported 2 cases of spontaneous rupture of the urinary bladder. The first case was secondary to an adjacent inflammatory lesion, and the second case to a vesical calculus.

Barnes and Steele[2] reported a case of rupture of an apparently normal viscus with no associated extravesical changes, or history of possible vesical overdistention. Their tally was the twenty-second of spontaneous rupture of a normal bladder that had been reported up to that time (1935).

Beresford-Jones[3] reported a case of spontaneous bladder rupture in a 27 year old woman. No operation was performed. At autopsy an intraperitoneal rupture was found and the case reported as a 'true nonpathological spontaneous rupture of the bladder.'

Bacon,[4] in 1943, reviewed 147 cases of rupture of the urinary bladder and divided them into three groups: group 1, 102 cases due to external trauma; group 2, 40 cases complicating transurethral resection; group 3, 5 cases of spontaneous rupture (4 cancer). His summary states that the predominating symptoms and findings were: pain, shock, hematuria, retention of urine and skeletal injuries. Cystography was the most significant single diagnostic procedure.

Moroney[5] reported a case of spontaneous rupture in a tuberculous bladder. The patient was a 22 year old woman who complained of lower abdominal pain and anuria. Despite prompt and proper surgery, the patient died. At autopsy bilateral renal tuberculosis, together with ureteral and vesical involvement were found.

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[4] Bacon, S. K.: J. Urol., **49:** 432, 1943.
[5] Moroney, J.: Brit. J. Surg., **31:** 98, 1943-44.

Feigal and Polzak[6] reported 3 cases of spontaneous rupture: 1) a case of spontaneous rupture of the bladder in a man of 77, who died 12 hours after admission to the hospital; no operation was performed; 2) a case of prostatism and alcoholism in a 52 year old man; operation, including prostatectomy, was performed and recovery followed; 3) a case of spontaneous rupture following excessive alcoholic intake; operation was performed and uneventful recovery followed. This case closely resembles the one we are here reporting.

We would like to call attention here to spontaneous rupture of the overdistended bladder in a man in whom there was no evidence of trauma and there was no predisposing abnormality in the bladder, the bladder outlet or the urethra. Such a case, at least insofar as reported in the literature, is rare. Some of the reported cases of "spontaneous" bladder rupture in the male, often include data wherein either trauma or prostatic adenopathy obstructing the vesical outlet, without doubt played a responsible role.

CASE REPORT

R. T., No. 144442, was a 51 year old white platforman, who was admitted to the Emergency Room of the Lenox Hill Hospital at 10:00 p.m. on June 11, 1950. The history obtained from the patient was that on the afternoon of June 10th, a Saturday, he began to drink a large number of "beers," as was his usual weekend custom. At a subsequent interrogation he admitted having had at least 40 glasses of beer during the afternoon and evening of June 10. On admission, the patient stated that between the evening of June 10 and 10:00 a.m. of June 11, he did not know what had happened to him beyond the fact that he subsequently was told that friends had taken him home, and put him to bed at 3:00 a.m. on June 11. On "coming to" at 10:00 a.m. on June 11, he experienced severe, crampy lower abdominal pain, and was also unable to pass gas rectally or to urinate. Subsequently, the abdominal cramps became generalized. He was mildly nauseated, vomited once but was able to retain a small meal a few hours prior to admission. About 5 hours before admission the family doctor was called and was able to pass a rubber catheter with ease. Three hundred cubic centimeters of bloody urine were withdrawn. Immediate hospitalization was advised.

On admission the patient was obviously acutely ill. The temperature was 101.2 F, pulse 136, respiration 20, and the blood pressure 160/104. The skin was moist but warm. He complained bitterly of severe lower abdominal pain, which was dramatically accentuated in the recumbent position. A few ecchymotic marks over the skin of the arms and legs were noted, but careful examination revealed no evidence of recent or old trauma, of the chest, abdomen, genitalia or perineum. The abdomen was moderately distended. There were no visible peristaltic waves; intestinal sounds on auscultation were generally suppressed. There were no herniae. Marked tenderness was elicited suprapubically and toward the iliac fossae; the abdomen percussed dull up to the umbilicus. There was no costovertebral angle tenderness. No masses or organs were palpable. On rectal examination the prostate was normal in size, shape and consistency; a hard stool was present in the rectal ampulla. The white blood count on admission was 14,000 with 90 per cent polymorphonuclear leukocytes. A plain film of the abdomen, taken immediately, yielded no further significant information; moderate generalized distention was noted.

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[6] Feigal, W. M. and Polzak, J. A.: J. Urol., 56: 196, 1946.

It was assumed that this patient was suffering from acute urinary retention, probably due to an enlarged prostate gland obstructing the vesical outlet. A No. 18 soft rubber catheter was easily passed into the bladder, without any obstruction being encountered. Eight hundred cubic centimeters of bloody urine were withdrawn. This, however, did not relieve the patient's symptoms, and his severe pain continued without let-up. His general condition worsened during the ensuing 3 hours, and the signs of tenderness and guarding, originally confined to each lower quadrant, were now noted in the flanks, and upper abdomen. At this juncture it was assumed that he had a ruptured bladder despite the absence of obstructive disease and of evidence of direct trauma. The patient was taken to the cystoscopy room, and cysto-urethrography performed (fig. 1). The first film was taken after the injection of 75 cc of a 5 per cent sodium iodide solution into the bladder, through a soft rubber catheter. The second film was taken after the withdrawal of the catheter and following injection of 5 cc of a 40 per cent Skiodan solution into the urethra. These roentgenograms demonstrated the dye passing into the peritoneal cavity, from a small contracted bladder. Following the x-ray studies, a cystoscopy was done. No cystoscopic evidence was present

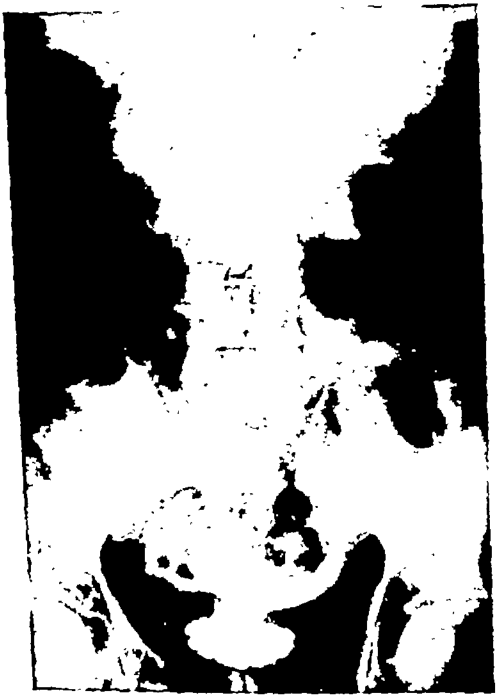

Fig. 1. Cystogram demonstrates a contracted bladder. The contrast medium enters directly into the peritoneal cavity, and is seen distributed along the pelvic peritoneum.

of trauma or of prostatic encroachment at the vesical outlet or into the posterior urethra. No stone or growth was seen in the bladder. The ureteral orifices were normal. In the upper post-trigonal region, however, directly in the midline, a large rent was seen extending through the entire thickness of bladder wall. The ragged edges of this rent were covered with clot, and a loop of intestine was plainly observed prolapsed into the bladder, as though to plug the opening.

A blood transfusion was begun. Under spinal anesthesia 5 hours after the patient entered the hospital, a midline suprapubic incision was made and deepened to the bladder. The reflection of peritoneum onto the bladder was dissected upward and the bladder entered fairly low, anteriorly. From within the bladder a sagittal rent in the dome, splitting the viscus for an estimated distance of 8 cm., was readily seen. A loop of small bowel and in addition a knuckle of the sigmoid, with its attached appendices epiploicae, were herniated into the bladder through the rent. The prostate was normal in size, shape and consistency, and there was no evidence of trauma, or of intrinsic disease of the bladder wall. Following inspection of the damage from within the bladder, the peritoneal cavity was entered, by incising the peritoneum above the bladder. A large amount of blood-tinged urine, found in the peritoneum, was aspirated. The incarcerated intestinal loops were replaced into the abdominal cavity. The anterior limit of the bladder rent was then extended until it joined the upper border of the cystostomy wound. A single linear defect in the bladder was thus created. This was closed with two layers of interrupted chromic catgut sutures, after a 40F open Pezzer catheter had been placed in the bladder and allowed to emerge from the lower angle of the incision. The peritoneum was closed about a Penrose drain extending from the pelvis. The incision was closed in layers and another Penrose drain was placed in the space of Retzius.

Postoperatively, the patient did well. The cystotomy catheter drained 300 cc of urine during the first 24 hours following operation. On the second day the patient voided some bloody urine. The peritoneal drain was withdrawn on the third postoperative day; the retropubic drain on the seventh day, and the Pezzer catheter on the ninth day. After removal of the Pezzer catheter the patient was placed on urethral catheter drainage for an additional 5 days. During the postoperative period penicillin therapy was maintained, with a changeover to chloromycetin on the fourteenth day, because of persistent low-grade fever.

The patient was discharged on the twenty-third postoperative day. Immediately prior to discharge cystography was repeated. Four hundred cubic centimeters of a 5 per cent sodium iodide solution were instilled through a urethral catheter into the bladder by gravity, and positional roentgenograms were taken. These films demonstrated a smooth bladder contour, except for two shallow outpocketings, superiorly.

COMMENT

Overdistention to the point of severence of the bladder epithelium, musculature and peritoneum occurred in the absence of trauma, of obstructive disease at the vesical outlet and urethra, and of intrinsic-mural vesical disease. In such a

ie mechanism must be accepted as spontaneous. It should be emphasized
nere was no evidence of prostatic enlargement on rectal examination, on
erization, on cystoscopy, and at operation.

w comments are in order concerning the diagnosis and management of this
The diagnosis was clinically suspected because of local and systemic signs
ymptoms of expanding lower quadrant peritonism, over a 4-hour period,
iated with hematuria.

rupture of the bladder was presumed to have been present until proven
wise. Within a matter of several minutes cysto-urethrographic and cysto-
c studies were performed. The demonstration of dye in the pelvic peritoneum
-ray and of a vesical rent plugged by a loop of small bowel on cystoscopy, was
lusive and dramatic. At operation a combined extra- and intraperitoneal low
line incision was made, and the large longitudinal rent splitting the dome of
bladder was extended to the cystostomy incision. The single vesical defect
then repaired in two layers. The peritoneal drain, placed as a precautionary
sure, was removed on the third postoperative day, after the culture taken
peration, of the intraperitoneal urine, had been reported sterile.

The mortality rate in rupture of the bladder has been strikingly high in most
orts, frequently over 50 per cent. However, most reported deaths occurred in
group of intraperitoneal ruptures and before the introduction of our present
chemo-therapeutic and antibiotic drugs. As in the management of a rup-
ed viscus anywhere in the body, early diagnosis is of vital importance.

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TRAUMATIC VESICOVAGINAL AND RECTOVAGINAL FISTULAS

SYDNEY S. BAIRD AND A. D. GREEN

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This is the report of the injury and treatment of a 7 year old white girl. While playing in her yard, she fell about 6 feet to the ground and, in doing so, struck a pair of pliers (fig. 1, *A*). Her knee hit the pliers first and caused them to turn somewhat so that one arm of the handle struck her in the perineum.

Examination showed her to have suffered a superficial wound at the edge of the anus. This wound, in its entirety, could be completely inspected and seemed to be of no importance. However, urine was seen to be coming from the vagina: hence, the child was hospitalized, an anesthetic given, and a more thorough examination made.

Cystoscopy revealed two pieces of cloth to be protruding upward in a wound in the bladder floor just back of the trigone. The remainder of the bladder, as well as the urethra and ureteral orifices, appeared to be perfectly normal. The scraps of cloth were easily removed transurethrally by using small cystoscopic forceps. The scraps were each found to be about 1 centimeter square; one was from the child's shorts and the other from the panties she was wearing at the time of the accident (figs. 1, *B* and 2).

Vaginoscopy (using the McCarthy panendoscope) showed two wounds to be present, one in the anterior wall (into the bladder) and the other posteriorly (into the rectum).

Proctoscopy was then done. A rather large wound was found in the anterior rectal wall about one inch inside the anus. The superficial perineal wound at the edge of the anus was noted and, as previously suspected, was of no consequence.

These findings clearly explained the method in which the child had been injured. The handle of the pliers had struck the child's perineum, slipped into the rectum, pierced the rectovaginal septum, traversed the vagina, and ruptured the vesicovaginal wall just back of the trigone. And during all this process, two pieces of cloth which had been punched out of the child's clothing were carried on the handle of the pliers into the urinary bladder.

Inspection of the wounds from the bladder, as well as from the vagina and rectum, showed them to be somewhat ragged and rather large, as can be judged from the photograph of the pliers (fig. 1, *A*). However, the wound edges were seen to fall together in excellent approximation. Hence, we decided to see what could be accomplished by radically conservative treatment. We believed that the child might have a more normal result if the wounds could be allowed and encouraged to heal by primary union rather than following colostomy and the surgical closure of the vesicovaginal and rectovaginal fistulae.

Accordingly, a Foley catheter was introduced through the urethra into the bladder for constant drainage, and control of gastro-intestinal activity was gained to some extent by the use of paregoric and a nonresidue diet. Last, but

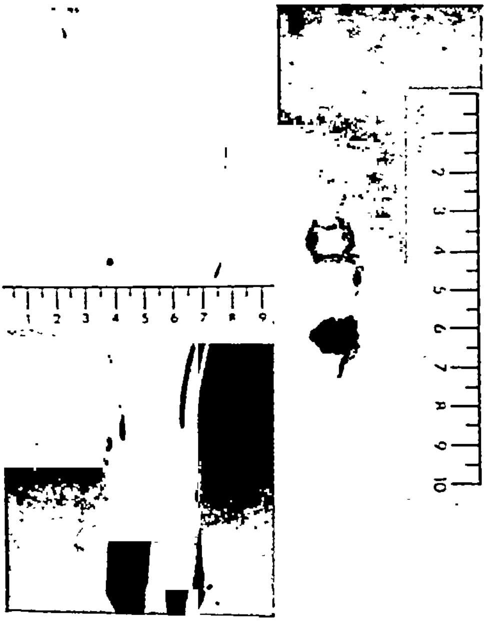

Fig. 1. *A*, pliers involved in accident. *B*, pieces of cloth pushed into child's bladder by handle of pliers.

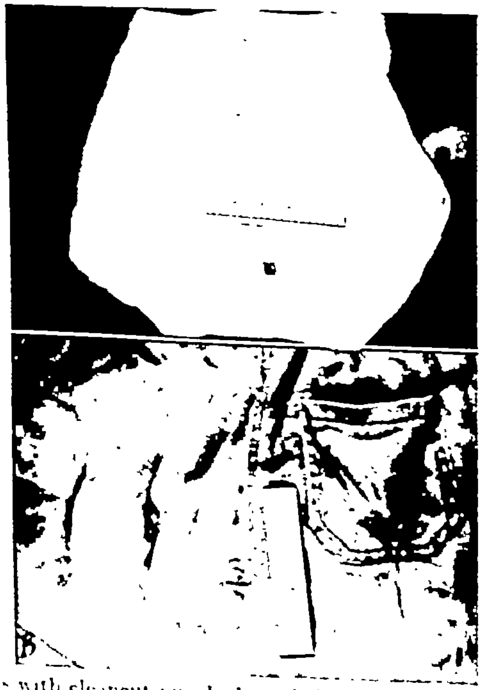

Fig. 2. *A*, panties with clean-cut punched out hole; *B*, shorts of heavy cloth with hole made by handle of pliers.

not least in importance, was the matter of preventing infection. For this purpose we gave dihydrostreptomycin (0.25 gm. every 6 hours); penicillin (100,000 units aqueous every 3 hours), later changed to duracillin-F (400,000 units every 12 hours); and cremothalidine (10 cc every 4 hours, making the 24 hour total to be 12 gm.).

From the standpoint of controlling the urinary outflow and infection, we were highly successful. The child was admitted to the Texas Children's Hospital (No. 10611) on May 26, 1951, shortly after her accident occurred. On entrance, her temperature was 100F, but never thereafter during her 29 day hospital stay was it higher than 99.2F. From the time that the Foley catheter was placed through the urethra into the bladder, all urine was delivered to the sterile bottle, and there was no longer any urinary drainage from the vagina or rectum.

In the matter of controlling gastro-intestinal activity, however, we encountered difficulties. Following her admission to the hospital on May 26, we gave her paregoric (1 dram twice daily). She had one soft yellow stool from the vagina on May 28 and on May 29, but none on May 30. However, on May 31, there were four such vaginal stools, another on June 1, and again on June 2. By this time, the paregoric dosage had been increased to 2 drams 3 times daily, and it seemed that a colostomy would have to be done. But local examination showed no evidence of infection, and three stool cultures were negative. No feces appeared on June 3, and the small amount which was passed on June 4, came via the rectum and anus, with no further stools passing through the vagina. Subsequent more or less normal bowel movements occurred on June 8, 9, 10, 15, 16, 17, and 18.

On June 22, the child was again anesthetized and subjected to cystoscopy, vaginoscopy, and proctoscopy. Except for mild redness in the region of the previously noted wounds, all findings were surprisingly normal.

After two normal days of being on her own with no catheter and no medications, she was discharged from the hospital and has been in good health with normal bladder and bowel function ever since.

SUMMARY AND CONCLUSIONS

The history of a seven year old girl with traumatic rectovaginal and vesicovaginal fistulas is briefly presented.

Ultraconservative management was employed. This included constant bladder drainage with a Foley catheter, paregoric and nonresidue diet, and adequate antibacterial agents (25,400,000 units of penicillin and 16,050 milligrams of dihydrostreptomycin were given).

The more important parts of this regimen would seem to be the control of infection and the prevention of urinary fistula.

The fact that feces passed per vaginam for a week after the accident and per rectum at rather frequent intervals thereafter did not seem to interfere with ultimate healing.

The end results were surprisingly good.

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DIVERTICULUM OF FEMALE URETHRA; AN IMPROVED TECHNIQUE OF SURGICAL EXCISION

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In reviewing the literature on diverticulum of the female urethra, one is impressed with the great variation of its incidence as reported by numerous authors. Higgins and Roen reported that only 7 cases were seen at the Cleveland Clinic in the 22 years between 1921 and 1943. Cook and Pool in 1949 reported 71 cases from the files of the Mayo Clinic as of January 1, 1948. Wharton and Kearns reported only 30 cases seen at Johns Hopkins from 1890 to 1949; they added, however, 14 cases of suburethral cysts and 8 of suburethral abscess as both of these conditions have not been clearly differentiated clinically from diverticula of the female urethra. There is convincing evidence that this lesion is one of those conditions which is found in direct proportion to the avidity with which it is sought. It is interesting to note that one of your members, Dr. William N. Taylor, read a paper on the subject before this Section in 1948 with the report of 23 cases. In a recent communication to the members of the Urologists' Correspondence Club, he mentioned 7 additional cases he has seen within an 18-month period, or a total of 30 since 1941. Evidently he is finding them relatively frequently, because he is diverticula conscious when dealing with complaints involving the urethra in women.

Diverticula of the female urethra may be either congenital or acquired. The majority apparently are of the latter type and may be due to several causes, such as the trauma of childbirth; infections of urethral glands with sealing off of the opening to the urethra with the formation of abscess and re-establishment of the communication; instrumentation of the urethra, especially deep electrocoagulation of urethral lesions; or they may be secondary to urethral stricture or to a urethral stone. Some authors have questioned the congenital origin of diverticula, but on the other hand the idea seems definitely refuted by the report of Johnson, in 1938, of one in a newborn infant. In one of the author's cases a urethral diverticulum was the site of the orifice of an ectopic ureter which drained the upper segment of a duplicated right kidney—very obviously a congenital diverticulum. Higgins and Rambauseck in 1945 stated that congenital diverticulum of the urethra in women is comparatively rare and that the literature revealed only 2 cases.

In my own files are found the records of 10 cases. Their ages varied from 31 to 44 years, averaging 36.6 years. All of these were married women and 7 had borne children. Diagnosis of the lesion is not difficult if four important points are kept in mind and I refer to a careful history, thorough physical examination, urethroscopic inspection and urethrography.

Read at annual meeting, North Central Section, American Urological Association, Milwaukee, Wis., October 12-14, 1950.

SYMPTOMS

Small urethral cellules may be asymptomatic as are larger pouches until there is a supervening infection. There is evidence that once a diverticulum becomes infected it is troublesome continuously or at frequent intervals thereafter. The most common symptoms are terminal dribbling of urine especially in the standing position, the appearance of a vaginal mass, digital pressure on which will cause the escape of urine or pus from the urethral meatus. Dyspareunia is very common and occurred in 5 of the 10 cases seen by the author. Frequency and dysuria are usual and occasionally the inflammatory process will invade the bladder with the symptoms of acute cystitis and not infrequently an ascending type of pyelonephritis will occur characterized by chills and fever. In a critical review of the 10 cases seen by the author, it is interesting to note that although their average age was 36.6 years, the average duration of symptoms was only 31 months, varying from 6 months to 9 years. The relatively short history would indicate that these diverticula were present in the form of a urethral cyst or some such type of sterile lesion long before infection and symptoms of an inflammatory nature became evident.

DIAGNOSIS

Definite recognition of the lesion depends upon discovery of its orifice within the urethra or demonstration of the diverticular sac visually in the roof of the vagina or by roentgenography. Usually the opening of the diverticulum may be seen in the middle third of the urethra in the midline but, as reported by Cook and Pool, it occasionally occurs in the roof of the urethra, a finding in 2 of the 71 cases they reported. The orifice of the sac may be extremely small or even pinpoint in size. In such cases the technique for urethrography described by Taylor may be useful and consists of filling the urethra with a radiopaque medium under pressure. This is accomplished by tying a silk ligature distal to the bulb of a 20F Foley catheter and then cutting an orifice immediately proximal to the bulb. The catheter is introduced into the bladder, the bulb is distended and is drawn snugly against the sphincter. The air is forced out of the catheter and the meatus is pinched about the catheter as the urethra is filled with the medium. The procedure works better when the patient is anesthetized so that an Allis forceps can be used to pinch the meatus about the catheter. This method has been useful in demonstrating diverticula when the orifice is not visible and undoubtedly accounts for Taylor's recognition of the lesion in an unusually high incidence of cases in which the symptoms were suggestive of the presence of the disease.

If the orifice of the sac can be visualized and a ureteral catheter can be introduced and coiled within it with or without injection of radiopaque medium, the size and extent of the diverticulum are readily demonstrable roentgenologically. This was possible in 7 of the 10 cases seen by the author but in 3, roentgen demonstration of the diverticulum was not possible. It is interesting to note in this connection that the largest diverticulum seen in this group with an estimated capacity of 60 cc, catheterization of the ostium was found impossible. Because of the fairly large mass in the roof of the vagina this patient shortly before had been subjected to a cesarean section.

SURGICAL MANAGEMENT

Small urethral cellules and even asymptomatic diverticula which are discovered incidentally may be disregarded from a therapeutic standpoint, but the patient should be told of the existence of the lesion and warned that at some future time troublesome symptoms may develop. In those cases in which the inflammatory features of the disease have appeared, it seems that complete surgical excision of the diverticulum and repair of the urethra are necessary. Several techniques are described in the literature, among which may be mentioned that of Furniss who, in 1935, advocated the incision of the sac from the

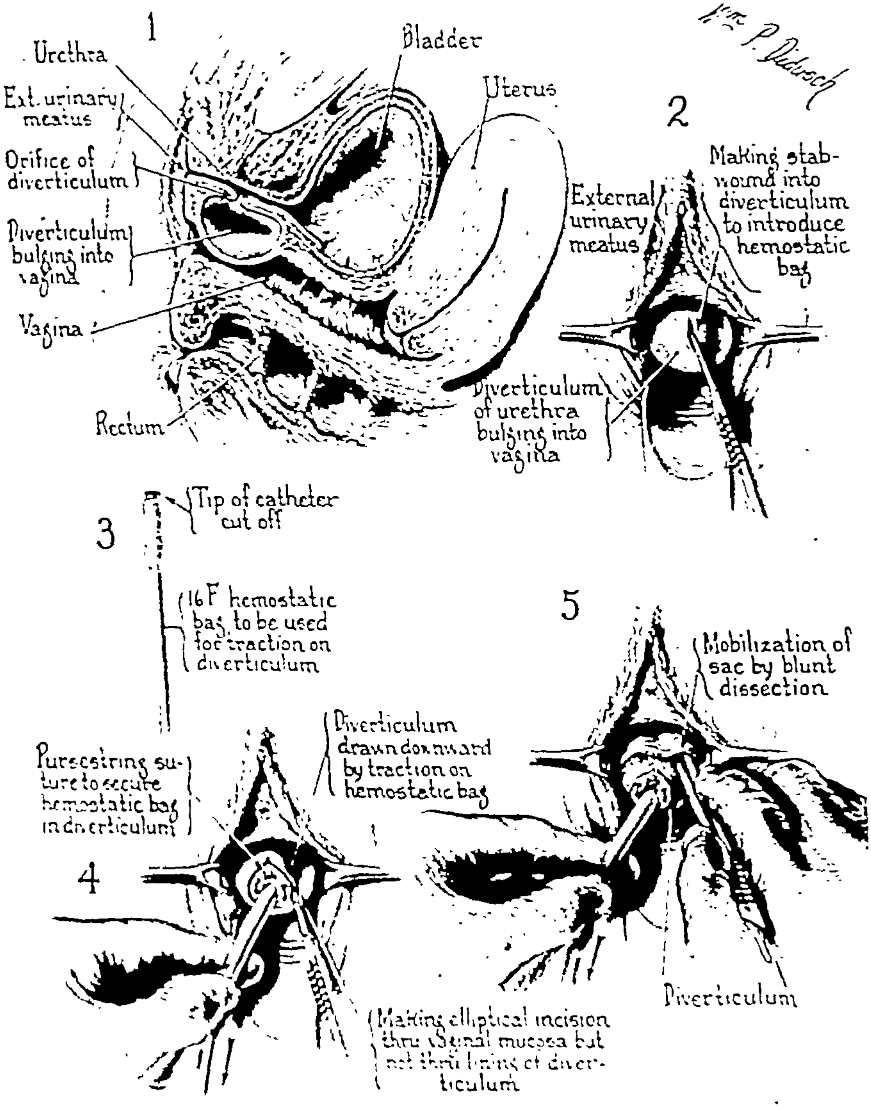
1
Urethra
Ext. urinary meatus
Orifice of diverticulum
Diverticulum bulging into vagina
Vagina
Rectum
Bladder
Uterus
Wm P. Didusch
2
External urinary meatus
Making stab-wound into diverticulum to introduce hemostatic bag
Diverticulum of urethra bulging into vagina
3
Tip of catheter cut off
16F hemostatic bag to be used for traction on diverticulum
Pursestring suture to secure hemostatic bag in diverticulum
4
Diverticulum drawn downward by traction on hemostatic bag
Making elliptical incision thru vaginal mucosa but not thru lining of diverticulum
5
Mobilization of sac by blunt dissection
Diverticulum

FIG. 1 Author's operative technique of urethral diverticulectomy

vaginal side with electrocoagulation of the mucosa and packing with gauze; if a sinus remained, secondary plastic closure was advised. In 1938, Young proposed the passage of a sound per urethram into the orifice of the diverticulum which aided in recognizing the sac in the roof of the vagina and served to facilitate its complete transvaginal excision. In 1938, Hunner described a somewhat similar technique and after removal of the sac, advised trimming the redundant vaginal mucosa from one side only and then bringing the opposite vaginal flap across to the remaining margin for closure, thus leaving no sutures superimposed after

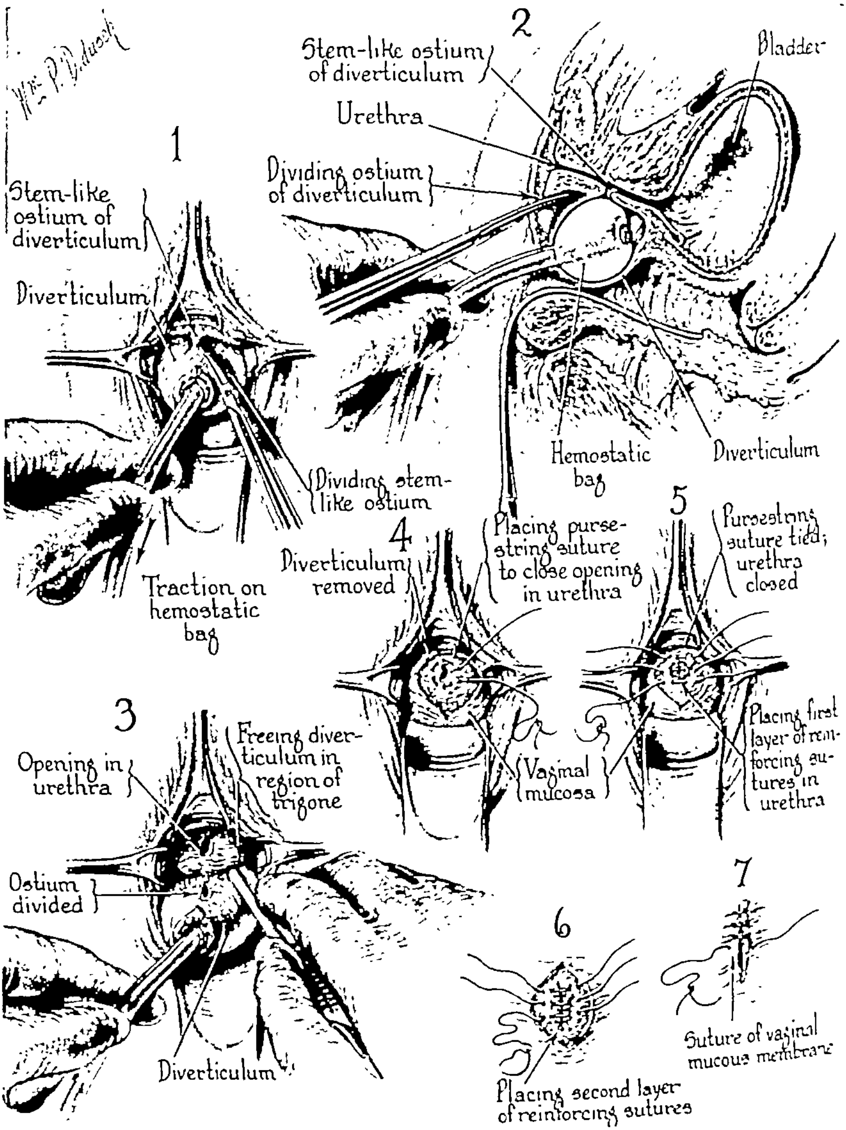
Wm. P. Didusch
1
Stem-like ostium of diverticulum
Diverticulum
Dividing stem-like ostium
Traction on hemostatic bag
2
Stem-like ostium of diverticulum
Urethra
Dividing ostium of diverticulum
Bladder
Hemostatic bag
Diverticulum
3
Opening in urethra
Freeing diverticulum in region of trigone
Ostium divided
Diverticulum
4
Diverticulum removed
Placing purse-string suture to close opening in urethra
Vaginal mucosa
5
Pursestring suture tied; urethra closed
Placing first layer of reinforcing sutures in urethra
6
Placing second layer of reinforcing sutures
7
Suture of vaginal mucous membrane

FIG. 2. Author's operative technique of urethral diverticulectomy

closure of the urethral defect. In 1939, Hyams and Hyams advised packing the sac transurethrally with a strip of gauze or rib dam, thus converting it into a semi-solid tumor, facilitating its dissection and accurate excision. In 1944, Menville and Mitchell described a procedure in which traction on the bladder neck with a balloon-type catheter or prostatic retractor appeared to be an advantage. In 1949, Cook and Pool, in their report of 71 cases treated at the Mayo Clinic, stated that the insertion of a small ureteral catheter transurethrally through the orifice allowing it to coil in the sac, is an aid to the surgeon in recognition of the lesion.

In reviewing the results of treatment, however, there is evidence that urethrovaginal fistula will occur unless the entire sac is excised. Such fistulas occurred in 2 cases of 5 reported by Higgins and Rambauseck in 1945. The author has seen an extensive vesico-urethrovaginal fistula resulting from the excision of a diverticulum elsewhere in which repair of the urethral defect did not hold. In the 10 cases reviewed a urethrovesical fistula occurred in one which responded favorably to its secondary excision and repair. This occurred before the operative technique described here was adopted. It goes without saying that unless the entire sac is completely eradicated and the urethral defect properly repaired, the functional result will not be satisfactory.

AUTHOR'S TECHNIQUE

Since 1944 the operation described here has been employed with uniformly good results. The technique portrayed by drawings by Didusch requires no detailed description (figs. 1 and 2). In brief, the operation consists of deliberately inserting a 16F Foley catheter into the sac in the roof of the vagina through a small stab wound which is secured by a pursestring suture. The tip of the catheter should be removed. The site of the insertion, including the pursestring suture, is then excised by a small elliptical incision, permitting exposure of the sac wall. The distended Foley bag not only converts the diverticular sac into a semi-solid tumor but it permits traction, facilitating the dissection. If a catheter or sound has been previously inserted through the urethra, the ostium of the sac is readily recognized when it is transected and permits its more accurate closure, either by a pursestring or intermittent mattress suture. The peri-urethral tissues should be approximated in one or two additional tiers and finally the vaginal mucous membrane closed with or without the excision of any redundant margins. If excision of some of the vaginal mucosa appears desirable, Hunner's suggestion of excising only tissue on one side would appear advantageous as the final suture line would be off-set from those underlying it. It has been our custom to leave in an inlying urethral catheter from 5 to 7 days. It has not been found necessary to divert the urine by suprapubic drainage as has been advocated by some authors. Finally, a snug vaginal pack incorporating a sulfonamide has been left in place for 48 to 72 hours. In the majority of cases the patients can be dismissed from the hospital from the seventh to the tenth day and they have been almost unanimous in their expressions of gratitude for the relief obtained as a result of excision of a diverticulum.

SUMMARY

A review of the incidence, types, symptomatology and diagnosis of diverticulum of the female urethra is presented together with an improved technique for its surgical excision. Unless all of the diverticular sac is removed, an unsatisfactory result may be expected. The author's technique facilitates recognition and removal of the entire sac wall and has been used with satisfaction in a limited number of cases.

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PROTRUSION OF THE FEMALE URETHRA

OSCAR DE BARROS SERRA DÓRIA

We had the second case of protrusion of the urethra and as it was treated with success by an unusual method we find it interesting to call the general attention to this easy, safe, successful and almost unknown way of operating such a pathologic entity.

Many operative and nonoperative methods have been invented to deal with protrusion of urethra, and we may say that almost every physician who had a case tried to solve the situation in his own way. Many of the methods mentioned in the textbooks on surgery and urology are delicate and intelligent, but undoubtedly they are not always practicable and sometimes the final results are unsatisfactory. To account for these and for the impracticability of several operations it is only necessary to remember that in the great majority of cases the physician sees a protruded urethra in an advanced state when it is edematous, bluish in color, necrosing, infected.

So, only to mention the chief methods, we know that fulguration of the everted parts is followed by the danger of retraction (linear fulguration, after Van Buren;[1] fulguration at the four points of the compass (Livermore);[2] complete fulguration of the everted mucosa[3]); we know the difficulty of applying in an edematous and bleeding protrusion the methods of Kleinwächter,[4] Leal,[5] Kelly-Burnam[6] and Johnston;[7] the impracticability of the operation of Keefe,[8] Emmet[9] and of Hepburn[10] when the first condition, the reduction of the protrusion, is not attained.

In a previous article in which we studied thoroughly this subject, mainly the various methods of treatment,[11] we reported a case in a girl 5 years old in whom we used an operation similar to that devised by Reid[12] for irreducible prolapse of the rectum. Subsequently, thinking in the originality of the method, we reviewed the literature and we saw that as late as 1930 (therefore 3 years before Reid) Pollak and Klement[13] had cured their patient in the same way but aiding fulguration after the ligature. They say that Stoekel advised such method before them but they give no reference. This process which we called slow extirpation by continuous elastic ligature is executed as follows:

Insert a resistent, thick walled, Nelaton catheter into the bladder, which is quite easy in these cases. The number of the catheter obviously varies according to the normal diameter of the urethra. Afterwards pass a thread of silk not very thin (No. 2 or 3) around the base of the protrusion just in the neck. Then tie the silk thread with hard pressure enough to compress the everted part against the sound which in turn, on account of its elasticity, will maintain a continuous tension. The catheter will be also fixed by this way. Within a variable time (1 to 8 days) which depends on several factors such as size of the protrusion, state of the tissues, etc., together with the sound will be eliminated the everted part that little by little suffers a dry necroses and falls away leaving a reconstructed meatus without any retraction. Besides many other advantages we may say that this method is of rapid, easy and safe execution, that it is appliable in all ages and in every case, even in the infected and gangrenous ones, that it has no danger and gives no retraction.

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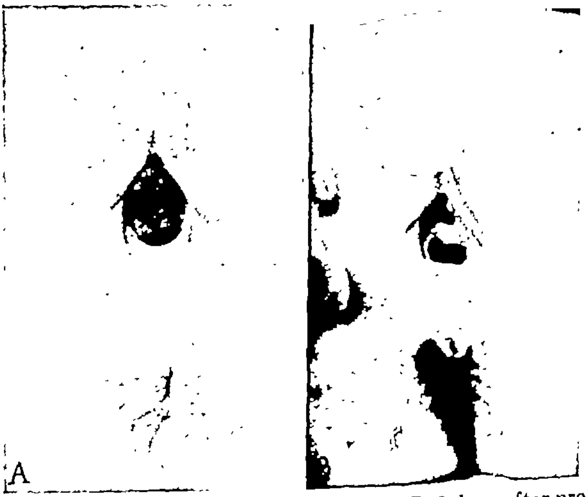

FIG. 1. *A*, protrusion of urethra in a girl 7 years old. *B*, 2 days after protrusion was eliminated.

We think that this forgotten procedure deserves more consideration and that the above mentioned advantages make it worthy of wide publication.

REPORT OF OUR SECOND CASE

D. de J., 7 years old, white, Brazilian, born and living in Ipiguá (São José do Rio Preto, State of São Paulo), called on us on September 12, 1948 together with her mother who informed us that her child was staining the clothes with blood. The child complained of nothing at all and answered that she had had no injury, strain on urine, cough, and so on. Her mother confirmed her statements saying she had no dysuria. Examination revealed a well constituted girl; nothing abnormal was found. Laying the child in gynecologic position and putting aside the labia majora we saw a round mass, bluish in color, oozing a blood-serous secretion, emerging between the labia minora (fig. 1, *A*). It measured about 1.5 cm. in diameter and presented a linear anteroposterior depression in its center.

We passed a tenaculum around it and verified that it was fixed in a circular groove, ring-shaped neck. In those maneuvers it was slightly painful. Raising the mass we could see perfectly the entire free hymen. Easily we inserted a rubber catheter through the central depression which brought clear normal urine. Its examination revealed only the presence of rare erythrocytes.

With the diagnosis of protrusion of the urethra, we resolved to use again the same process of slow extirpation by continuous elastic ligature which had given stupendous results in our first case. In the same day without anesthesia we inserted a No. 15 Nelaton catheter, and tied a No. 2 silk thread around the protrusion, just in the neck, which was tied with a pressure sufficient to compress it against the sound that was simultaneously held in its place by the ligature. The child tolerated the operation well and she rested in bed for 5 days, when the catheter fell away bringing together the protruded part which was reduced to a dried and contracted mass. The meatus was completely reconstructed (fig. 1, *B*), and micturition was quite normal. Sulfadiazine was used locally and orally. The child came for examination 4 months later saying she was all right. No sign of the old protrusion could be seen.

SUMMARY

The author reports his second case of protrusion of the urethra which was again treated with the best success by an old and forgotten way of operation. The method of treatment is described in detail.

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ACCIDENTAL TRANSECTION OF ALL CORPORA OF THE PENIS: REPAIR WITH GOOD RESULTS

KLINE A. PRICE

This case is presented for three reasons: 1) It is a urologic rarity; 2) it is doubtful that its counterpart exists with regard to management; 3) its far-reaching possibilities offer a potentiale which, in view of the recent advances in eye, bone and skin banks and replacement surgery in renal lesions, makes most tenable its inclusion into the armamentarium of the urologist who is so frequently confronted by irreversible penile pathological changes involving the distal, the middle and often the greater portions of the proximal thirds.

A review of the literature exposes a dearth of material on the problem of penile injuries. Possibly it is, as Ehrich has stated: "The scarcity of recorded cases of penile injury leads one to believe either that the penis is seldom injured or else the injuries are deemed of insufficient importance to report." Ehrich (1929) reported two unusual penile injuries, one of which had features similar to that reported in this article. A factory worker operating a circular saw received injuries which entered the scrotum on the left, split the testicle, denuded the penile skin and, 1.5 cm. behind the coronary sulcus, severed the penis with the exception of a strand of tissue on the dorsum about 0.7 cm. wide and 0.2 cm. thick. The wound entered the mons and the abdominal wall, but missed the peritoneum. After vessel ligation and left orchiectomy, the severed urethra was repaired over an indwelling catheter with No. 1 plain catgut. The fibrous coverings of the corpora cavernosa were united with No. 1 chromic catgut. The skin was repaired. The next day, a needle stuck into the glans gave slight pain and a drop of blood. After uneventful convalescence, the catheter was removed on the tenth day; grafts were used to hasten healing. When seen 2 years later, the organ was normally shaped; in erection it was 1 cm. shorter than normal; the urethra was narrow at the repaired area. There was normal physiologic function for the patient had recently become a father.

Dodson reported the case of a young child who was run over by a light truck. The body of the penis, including the urethra, was torn from the glans and forced under the skin of the pubis. After clot evacuation through an incision on the ventral surface, the penis was brought down and sutured to the glans with interrupted sutures of plain catgut. An indwelling urethral catheter served as a splint and to divert the urine. About half the glans penis sloughed away because of injury to the blood supply; otherwise healing occurred satisfactorily.

Abstracts of other articles on penile injury, though interesting, failed to show features which were sufficiently related to that herein reported to justify inclusion.

CASE REPORT

The 56 year old patient, whose case is herein reported, was first seen by the writer who answered an emergency consultation call to the main operating room for advice on the management of the patient. The patient was already under anesthesia. The entire corpora cavernosa and corpus spongiosum were found to be completely severed approximately 2 cm. in front of the pubis, with merely the ventral, left and a portion of the right penile skin serving to join the penis to the body. Access to that portion of the penis had been attained through an extended combined low hernial and upper scrotal incision.

Inasmuch as there was total disruption of the vascular supply and the continuity of the corpora in their entirety, with merely portions of the skin and subcutaneous fascias remaining undisturbed, it was first believed that completion of the amputation, with perineal implantation of the urethra, was the management of choice. However, since the amputation could be completed at any time dictated by the subsequent findings, a decision was made to re-anastomose the corpora and repair the wound anatomically.

Under general anesthesia, using No. 5-0 chromic catgut, the two ends of the corpus spongiosum were coapted over an indwelling latex catheter. The sutures did not penetrate the mucosa. The septum pectiniforme of the corpora cavernosa was reconstructed and then the inner and outer layers of the tunica albuginea. Release of the clamp which had initially been placed on the proximal corpora cavernosa at the discovery of the accident gave a gush of blood which was controlled by further suturing of the tunica albuginea to effect a watertight anastomosis.

The remaining wound was closed with black silk sutures. To prevent accidental removal of the catheter, since its importance in an indwelling capacity was so great, the catheter was anchored to the elongated prepuce with black silk. The penis was encased in ice to retard metabolism. Antibiotic therapy, sedation, and rigid catheter management were maintained with frequent inspection during the day for the cyanosis which would indicate gangrene. Slight temperature elevation, moderate hemorrhage from the operative site, and proximal penile edema marked the first few days of postoperative convalescence, with the sensation of pain on pricking the glans being the most important finding on the second post operative day. The ice encasement was discontinued on that day. By the sixth day, although a bleb associated with some darkening of the skin had appeared on the dorsum, the color of the penis generally had approached normal and the glans was quite sensitive to pinching. The sutures were removed.

On the seventh day, the penile catheter came out. Voiding was accompanied by a blood-tinged streamlet of urine from the operative wound near the base of the penis on the right side.

Because voiding continued to be accompanied by some slight escape of urine from the wound area, and since an area of slough had appeared at the wound area, an indwelling catheter was replaced and the wound cleared of its slough by dissection. Wound progress was satisfactory; the catheter was maintained until the twenty-first day postoperative when he was discharged with merely a minor seepage of urine from the operative site at each voiding.

During the follow-up period after discharge, a catheter was re-inserted for a short time. An occasional urethral dilatation was effected by his physician to 22F. The aberrant urinary stream had decreased to small drops which could be prevented by digital pressure.

It has been a little over 1½ years since the accident. The drops of urine still escape from the operative wound. His sexual life is described as perfectly satisfactory. His urethral caliber is adequate, although undetermined.

COMMENT

Because of the results obtained in this particular case, it is believed that a most valuable addition has been made to the ever expanding urologic horizon.

It is conceivable that many entities may be so managed, obviating the necessity for orthodox partial and complete penile amputations with the attendant disadvantage of the perineal urethrostomy. It is conceivable that sudden, traumatic death donors may be used for most willing recipients who are kept alerted for emergency surgery, where there is irreversible deformity of the glans, the distal, middle or proximal thirds incident to 1) localized malignancy, 2) healed but severely scarred chancroidal and other lesions, and 3) the dumbbell-shaped chronically fibrosed middle and distal thirds of the penis frequently associated with urethral stricture, provided the remnant is natural.

Its value in all types of accidental amputation or avulsion is without question, provided all other factors are adequate and equal.

It differs from Dodson's case since in his patient, half of the glans penis sloughed away because of injury to the blood supply. In the case presented, the organ is natural.

Ehrich's case presented similar aspects with regard to repair and end result.

It is possible that, in view of the disruption of the continuity of the urethra, routine management of the patient as a urethral stricture with dilatation to a normal lumen might completely eliminate the fistula. Propriety, however, has dictated a laissez-faire management for the moment.

SUMMARY

A case of accidental complete transection of the penile corpora cavernosa and corpus spongiosum has been reported. Surgical and postoperative follow-up resulted in complete physiologic rehabilitation. This is believed to be the first case of its kind in occurrence, management and results reported in the literature.

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PEYRONIE'S DISEASE ASSOCIATED WITH DUPUYTREN'S CONTRACTURE

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Among the diseases of the penis, Peyronie's disease occupies a very interesting and unique position when it is associated with Dupuytren's contracture. Kirby in 1850 was the first to describe this association.

Until recent years the surgeon treated Dupuytren's contracture and the urologist treated Peyronie's disease with very little inquiry as to whether both conditions might be present in the same patient. In 1928, Polkey found 22 cases of associated Peyronie's disease and Dupuytren's contracture in the literature.

The authors became interested in the associated occurrence of these two conditions and questioned patients presenting either disease in regard to the other.

Many of the patients seen on the surgical service with Dupuytren's contracture were frank to admit that the penis curved when erect, although this history would never have been given unless specific inquiry had been made. Likewise, many of the patients seen because of Peyronie's disease had definite Dupuytren's contracture, although they were not concerned about the condition of the hands.

In both conditions, the patient usually waits until the disease is rather far advanced before seeking medical care.

Heite and Siebrecht, in an effort to determine the incidence of Peyronie's disease in Germany, studied 6038 males in a camp recently and found 455 cases of Dupuytren's contracture, 14 cases of Peyronie's disease and 10 cases of Dupuytren's contracture associated with Peyronie's disease. They found that fibrosis of the male breast was also often associated with these two diseases. No women were in this camp so they believed that trauma could not have played a role in the etiology of Peyronie's disease. They felt that cessation of sex functions, poor nourishment and lack of sex hormone production in these patients might have been responsible for the high incidence found. They felt that in the tunica albuginea, there were certain embryonal developmental tendencies, which following stimuli, would react with proliferation of fibrous tissue and metaplasia. They observed that hormonal changes which occur in older men on a deficient diet might be responsible.

We wish to report the findings in ten patients who had both Peyronie's disease and Dupuytren's contracture.

The youngest patient was 48 years of age while the oldest was 67. The average age was 57 years. The youngest patient ever seen with Peyronie's disease at this clinic was 42 years of age while the oldest was 78. Other authors report the occurrence in much younger patients, but this has not been our experience.

Among the group of patients studied there were 5 farmers or ranchers, 1 salesman, 1 post office clerk, 1 refinery worker, 1 railroad conductor, and 1 university professor.

Three of the patients were first seen because of Dupuytren's contracture while four of this group were chiefly concerned with Peyronie's disease. Three patients were found to have both conditions on examination for diabetes, hernia and heart disease.

The etiology is unknown. Trauma, gout, diabetes, arthritis, old age, vitamin E deficiency, and hormonal changes in subcutaneous anlage have been advanced as factors in the production of both conditions. Frequently our patients noticed that Peyronie's disease first became evident after the death, divorce, or serious illness of the wife, or other conditions which required abstinence from sexual relations. All of the patients of Heite and Siebrecht were isolated in a camp.

In about half of our patients, trauma could have played a role in the etiology of both conditions, although in the other half this certainly could not have been true.

Penile induration and curvature along with some degree of Dupuytren's contracture was present in all of the cases studied in this group. Pain on erection occurred in seven and some loss of potency in four. Both hands were involved by Dupuytren's contracture in eight, the right hand in one, and the left hand in another.

Although frequent mention is made in the literature suggesting that heredity is an outstanding predisposing factor, we were unable to demonstrate this in our series. Numerous diseases were associated with these two conditions; however we felt that none played any role in the production of either Peyronie's disease or Dupuytren's contracture. One patient had duodenal ulcer, one a right inguinal hernia, one heart disease and four had benign prostatic hypertrophy.

PATHOLOGY AND HISTOLOGY

Many authors have described the histologic similarity between Peyronie's disease and Dupuytren's contracture. Twenty years ago Hertzler stated that the disease usually starts in middle life with an indurated area on the dorsum of the penis. The induration may occur on the side of the penis and cause a lateral curvature rather than an upright curvature. These growths arise from oblique discs involving the tissues of the corpora cavernosa and the septum between them. The lesion is hard yet elastic. The skin glides freely over it. When the organ is flaccid nothing can be seen on inspection. It is only on palpation and erection that the lesion becomes obvious. The lesions are made up of dense fibrous tissue, the bundles of which may interlace and form wavy bundles. Hertzler stated that they were very difficult to section and that the nuclei were small, sparse, and spindleform. In both conditions he found a lack of inflammatory cell reaction and felt that there was a definite relationship between the two conditions.

In 1946, Steinberg reported cures in 6 of 7 patients with Dupuytren's contracture, treated with vitamin E. He believed that early and moderately advanced Dupuytren's contracture could be successfully treated by vitamin E by mouth. He later found that some patients had recurrence after vitamin E had been discontinued. Scott and Scardino treated 23 patients with Peyronie's disease, six of these having both Dupuytren's contracture and Peyronie's disease with alpha-tocopherol with good results to fair response in all but 2 patients. The condition was unchanged in these two patients. This treatment was used with the consideration that Peyronie's disease might be secondary to vitamin E deficiency.

The patients in our series were treated with 100 mg. of alpha-tocopherol 3 times a day for 6 to 12 months. We observed no untoward effects from the administration of the drug over this period of time.

In most cases, the results were better than we had expected and the patients were satisfied with their improvement.

Four of our patients improved greatly and four moderately. Two felt that there was some improvement in both conditions.

Whether alpha-tocopherol improves these patients because of vitamin E deficiency or for some other unknown reason, we are unable to say. However, histopathologic and clinical studies of Peyronie's disease and Dupuytren's contracture have been made by several investigators and a great similarity between the two conditions has been found. Callomon discussed the etiology and pathogenesis of the two conditions in great detail in 1945. We should expect, therefore that any drug which benefits the one disease should also help the other.

We do not mean to infer by this paper that Dupuytren's contracture alone is treated by alpha-tocopherol at this clinic. Most of these cases have been operated on with good results by our surgeons. It has been our experience, however, that the treatment of Peyronie's disease by surgery, radium or x-ray irradiation gave results which were disappointing. Since most of the patients were benefited by treatment with alpha-tocopherol we feel that further investigation along this line is justified.

SUMMARY

Ten patients with Peyronie's disease associated with Dupuytren's contracture are reported.

The similarity between the two conditions is discussed.

Most of the patients were benefited by treatment with alpha-tocopherol and the results seem to warrant further investigation with this method of treatment.

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CARCINOMA OF PROSTATE IN YOUNG ADULTS

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Carcinoma of the prostate is a disease of old age. Few cases have been reported in which the diagnosis was made for patients under 40. This paper reports two cases in young adults: a 20 year old patient admitted to Walter Reed Army Hospital on March 24, 1950, and an 18 year old admitted May 19, 1950.

Kimbrough and Rowe[1] reported the carcinoma series of 78 patients hospitalized at Walter Reed during the decade 1940–1949. The youngest in the series was 43. This paper was presented at the meeting of the American Urological Association meeting, May 1950, at Washington, D. C.

The review of literature shows few cases under 40, only two under 30, one of which was 17.

Gardiner and Cummings,[2] in 1942, reported carcinoma of the prostate in a patient 17 years old. Wolff[3] reported 6 cases under 40, only one of which was under 30. In 170 cases reported by Moore[4] the youngest was 39. Gaynor[5] found one case under 40, in 1040 autopsies. In the analysis of 1000 cases reviewed by Bumpus[6] the average age was 65, the youngest 42; Wear and Schoenberger[7] found one patient 38, in a review of 436 patients.

CASE REPORTS

Case 1. A white man, 20 years old was admitted to Walter Reed Army Hospital March 24, 1950, by transfer from an Army station hospital. The onset of the disease was February 1, 1950, with a low back pain, for which he was treated at the dispensary and station hospital without improvement. No cause for the pain was found. He was transferred to Walter Reed Army Hospital March 24, 1950 with a diagnosis of schizophrenic reaction, paranoid type. The past history was noncontributory except for a weight loss from 183 to 147 pounds during the last 3 months. There was limitation of flexion of the back with lumbar spasm. At digital rectal examination March 31, 1950, the prostate was enlarged grade 2, stony, hard, nodular and fixed, the median sulcus obliterated. The intervesicular space was indurated and presented a sharp superior margin. The seminal vesicles were thickened and firm. Blood count reported 4 per cent juvenile myelocytes. The spleen was enlarged; x-rays of the spine suggested arthritic changes.

A sternal marrow biopsy was positive for anaplastic malignant cells. The acid phosphatase was normal, the serum calcium was 15 mg. per cent. Cytological examination was negative for malignant cells; perineal punch biopsy of prostate showed anaplastic malignant cells similar to those of the sternal marrow biopsy. Stilbesterol therapy, 20 mg. daily, was begun. The patient refused castration.

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A perineal section biopsy, involving a wedge shaped piece of the posterior lamella of the prostate, was negative for malignancy. This specimen did not include the lateral lobes of the prostate, nor the urethra. Paralysis of the legs was noted. Spinal block at D-10 indicated probable metastases.

Transurethral resection, attended by little hemorrhage, was done because of urinary retention. At operation it was noted that the lateral and median lobes were indurated and intruded into the prostatic urethra; the trigone was edematous and corrugated. The specimen removed showed anaplastic malignant cells.

Radiation therapy and castration, July 13, 1950, produced considerable amelioration of the pain. However, the course was progressively downhill, and the patient died August 9, 1950. Autopsy revealed metastases to the lungs, ribs, spine and pelvis. There was no liver metastasis.

Case 2. A 17 year old white soldier was admitted to Letterman Army Hospital October 18, 1949, because of frequency of urination, nocturia, 3 to 4 times, diminution in size and force of the stream. Two days prior to admission he had noticed marked swelling of the lower part of the abdomen. Catheterization produced 1400 cc of urine. The prostate examination revealed grade 3 enlargement of the gland, which was stony, hard, irregular and fixed. There was extension of the induration to the seminal vesicles and periprostatic tissue.

The laboratory studies, including acid and alkaline phosphastase, were normal. Skeletal survey was negative for metastasis. Excretory urogram showed bilateral hydronephrosis and a sacculated bladder. A perineal biopsy showed anaplastic tissue interpreted as carcinoma by the Armed Forces Institute of Pathology. The treatment consisted of transurethral resection and deep x-ray therapy.

The patient was transferred to Walter Reed Army Hospital May 19, 1950. On rectal examination at this time, the prostate was found to be enlarged, stony hard, fixed and protruding into the rectal lumen. Again, laboratory studies, except for blood urea nitrogen of 72, were normal. A metastatic nodule in the right lung field was observed on chest x-ray. The patient was suffering from severe pain and partial paralysis, which cleared dramatically following castration and stilbesterol therapy, making it possible to grant him a sick leave.

Upon his return, the pain recurred, though it was never as severe as prior to the castration. A paralytic ileus subsequently developed, and his course went rapidly downhill, to expiration October 14, 1950. Autopsy revealed prostatic carcinoma of very anaplastic nature with metastasis to lungs, pleura, lymph nodes, liver and involvement of the local tissues.

DISCUSSION

The two cases show several interesting features. Figure 1 is a high and low power view of the sections in case 1. Figure 2 is a high and low power view of the

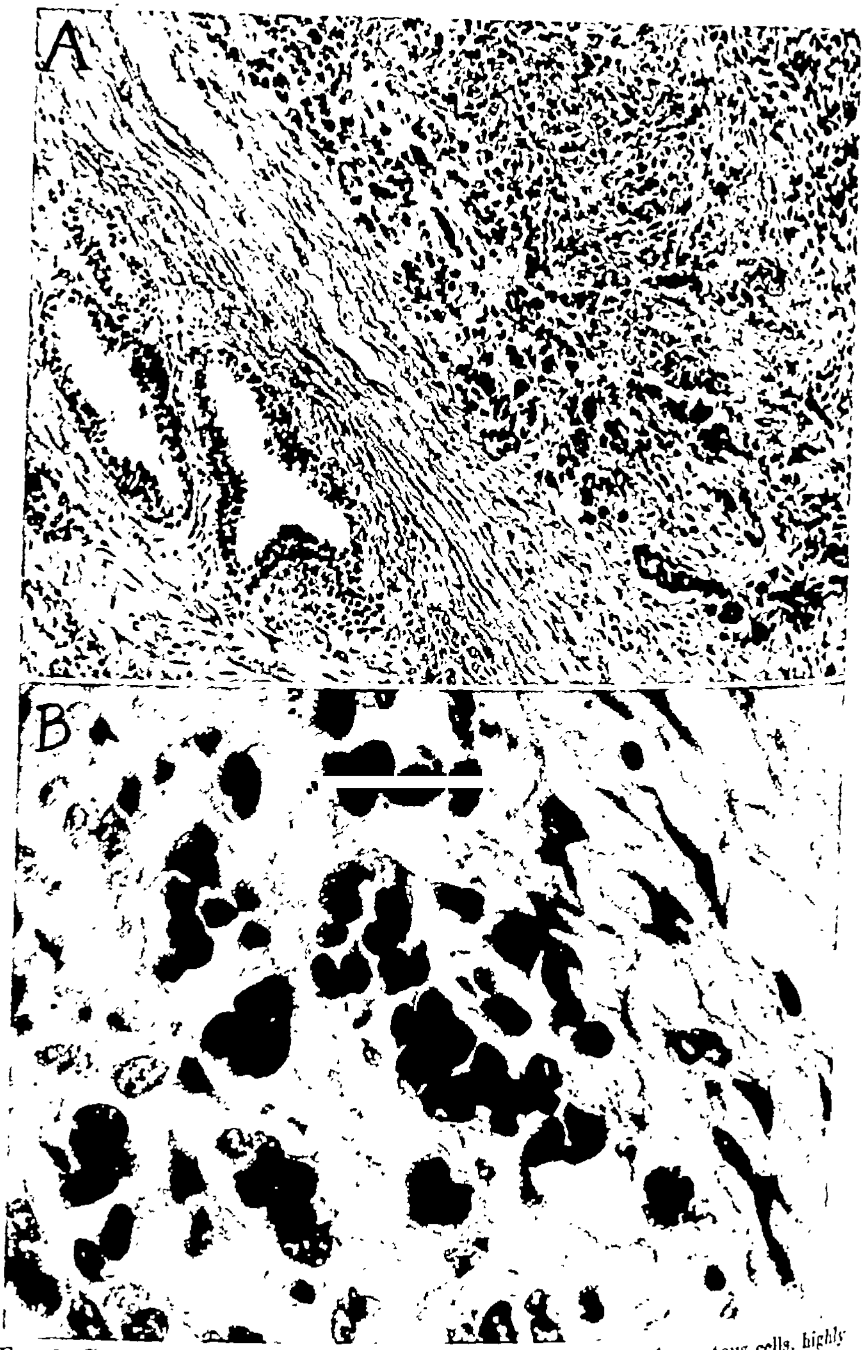

FIG. 1. Case 1. Section of prostate from autopsy showing carcinomatous cells, highly undifferentiated. *A*, low power. *B*, high power.

sections in case 2. These are sections of the prostate removed at autopsy.* The high power views show the marked similarity of the malignant cells. The cells

* Photomicrographs are through courtesy of the U. S. Army Illustration Service.

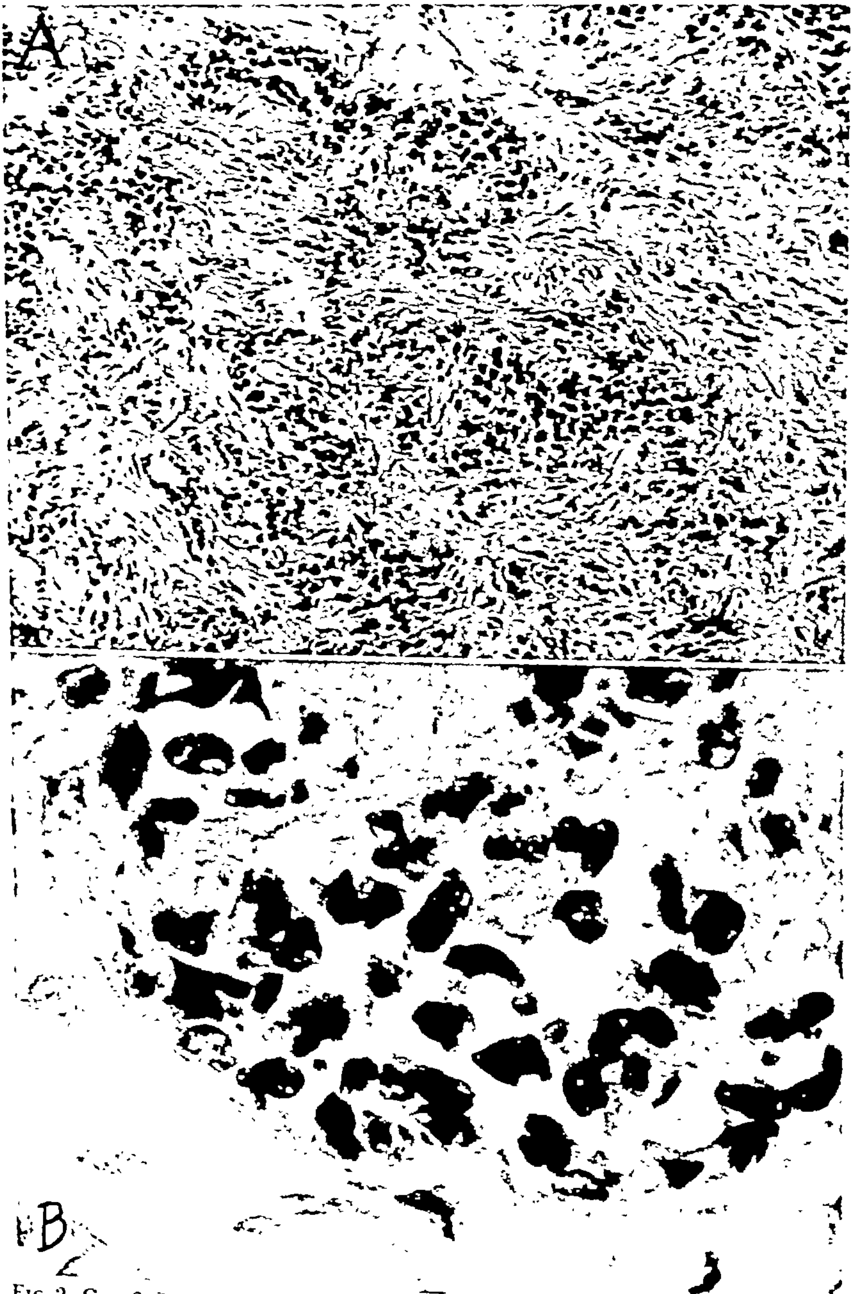

FIG. 2. Case 2. Sections of prostate from autopsy. These cells are highly undifferentiated and appear epitheloid although question of sarcoma has been raised. *A*, low power. *B*, high power.

are definitely epitheloid, and markedly anaplastic. There is variation in size and shape of nuclei with many mitotic figures present. The cells occur in nests, as seen in the low power view, and are highly undifferentiated.

From an endocrine standpoint these tumors are noteworthy. Both patients had only temporary relief of pain following castration and stilbestrol therapy. In the first case there was partial relief of pain from the time of castration to demise 3 weeks later. During this period the patient averaged 2 grains of codeine daily where morphine every 3-4 hours had been necessary prior to castration. In the second case there was relief of pain for 4 weeks, which was sufficient to allow the patient to leave the hospital for 30 days. Upon return the pain recurred but was never as severe as prior to castration.

It is also noted that in neither patient was there an elevation of the acid phosphatase although bone metastases were present for a considerable time prior to death. It has been observed that the acid phosphatase is increased in carcinoma of the prostate gland with metastasis only if the cells are well differentiated. On the other hand, highly undifferentiated prostatic cancer produces very little if any of this enzyme. It is believed that no elevation of the acid phosphatase should be expected in tumors of this degree of anaplasia.

That the diagnosis was difficult and not suspected is seen in the case histories. The first patient was treated as an orthopedic and finally a neuropsychiatric problem before the diagnosis was first suspected from a sternal marrow puncture done because of anemia. It was only then that a rectal examination was performed. The second patient was considered as having a prostatic abscess and there was complete urinary retention before medical advice was sought.

The differential diagnosis in prostatic enlargements of this age group should include: prostatitis, acute, chronic, specific, and nonspecific; abscess of prostate, perirectal abscess, sarcoma, and gumma. The biopsy will usually make the diagnosis but it should be stressed that the biopsy must include the whole thickness of the prostate. In the first patient the transurethral biopsy was positive whereas biopsy of the posterior lamella was negative.

SUMMARY

Two cases of anaplastic carcinoma in young adults, ages 20 and 18, are presented. In the younger, the carcinoma was actually first diagnosed before his eighteenth birthday. Photomicrographs showing the anaplastic epitheloid cells are presented. The interesting features of these cases are: 1) extreme youth, 2) minimal endocrine response, 3) lack of elevation of acid phosphatase, 4) rapid course of the disease.

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CYSTS OF THE TUNICA ALBUGINEA TESTIS

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Cysts involving the tunica albuginea testis are rarely seen in urological practice. In over 46,000 cases recorded in the Brady Urological Institute of The Johns Hopkins Hospital there are only three such cases. This lesion has not been described in the urological classics such as Cooper, Cabot, Thorek, Young, or Lowsley and Kirwin. Frater (1929) describes a case found at autopsy, and also reviews the brief literature on the subject, including that of cysts involving the testicular parenchyma. He points out that cystic disease of the testicular substance must be differentiated from that involving only the tunica albuginea. It is this latter, more uncommon disease that is discussed here.

The three cases in the Brady Institute files are summarized below. Case 2 was seen by the author in the Out-patient Clinic. Case 3 was seen by the author when he was a house officer on Dr. W. W. Scott's service on which the patient entered the hospital.

CASE REPORTS

Case 1. (J. H. H. No. 155,454; B. U. I. No. 27634.) A 55-year-old man admitted to the urological service of Dr. H. H. Young on November 27, 1938, because of "uncomfortable feeling in the groin and in the back" for the past 8 years. During these years he had received prostatic massages for a "congested prostate" and had thereby been temporarily relieved of the back pain. He denied that he had had gonorrhea or any acute scrotal swellings. He had had no scrotal or testicular pain or discomfort. Significant physical findings were confined to the right testis and epididymis. There was marked induration and enlargement of the globus major and the testis was thought to be essentially negative. Scrotal exploration was carried out by Dr. Young. Over the surface of the testis there were several cysts less than 1 cm. in diameter. One, however, was apparently multilocular, 2 by 2 cm. in size, containing clear fluid. Right orchiectomy was performed. The postoperative course was uneventful and the patient's back pain subsided.

Pathological diagnosis (Dr. Burkland): "Benign cysts of the testicle. Inflammatory reaction between seminiferous tubules" (fig. 1).

Case 2. (J. H. H. No. 430,274; B. U. I. No. 46637.) A 70-year-old Negro was admitted on the ward service of the Brady Institute on December 16, 1950, with the complaint of pain in the left testis and in the perineum of 6 weeks' duration.

The patient had been treated for central nervous system syphilis in 1947 and had primary optic atrophy. There was no history of gonorrhea, painful swollen scrotum, genital trauma or other significant urinary tract symptoms.

About 6 weeks before admission, the patient noted the onset of aching and occasional sharp pain in the left testicle, as well as "burning" in the groins and perineum. The patient was seen in the Out-patient Clinic at which time a 5 mm., moderately tender, markedly indurated nodule was felt on the superolateral aspect of the left testis. The left vas was moderately thickened. Following the patient's admission to the hospital, surgical exploration of the suspicious nodule was carried out by Dr. James Causey. A "pea-sized nodule" bluish in color was found, and because of the patient's age, an orchiectomy was performed. After an uneventful postoperative course the patient was discharged from the hospital. When seen 2 weeks later he was completely free from testicular, perineal, and groin pain.

Pathological diagnosis (Dr. D. C. McGoon): "... At one pole of the testis a cystic space is present, which is empty, and its wall is composed of a thin layer of condensed connective tissue with an inside lining of very flat cells. Diagnosis: Testicle: Cyst and atrophy" (fig. 2).

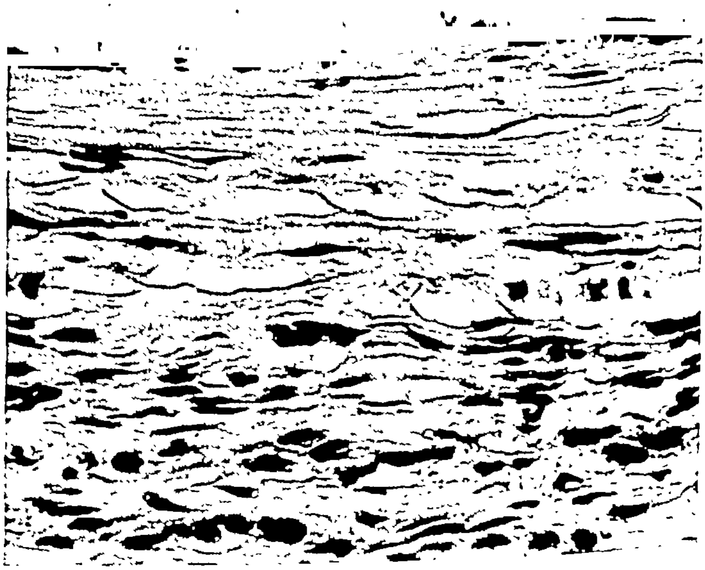

FIG. 1

Case 3. (J. H. H. No. 571,037; B. U. I. No. 47204.) A 44-year-old laborer entered Dr. W. W. Scott's service on May 3, 1951, complaining of painful swelling in the left testis of 3 to 4 months' duration. There was no previous history of gonorrhea or other genito-urinary disease.

For the past 3 or 4 months the patient had noticed the gradual swelling of the left testis with increasing pain therein. He had no other urological or systemic complaints.

Physical findings of interest were limited to the testes. The author's note made at that time states: "Right testis and epididymis cannot be clearly delineated because of multiple nodular swellings over their surfaces (these were nontender). ... Left testis and epididymis are also poorly delineated. There is an extremely tender nodule in the midportion of the testis adjacent to the epididymis. There are several smaller nodules nearby and superior to the larger nodule."

A preoperative diagnosis of cysts of the tunica albuginea was entertained.

On May 4, 1951, Dr. W. W. Scott explored the painful left testis and found a large cyst in the midportion of the testis and several small ones nearby (fig. 3). After aspirating the fluid within this cyst for culture (later reported as negative), the large cyst was excised and the tunica albuginea sutured. The smaller cysts were needled. The patient recovered without complication and was discharged in a few days definitely relieved from pain.

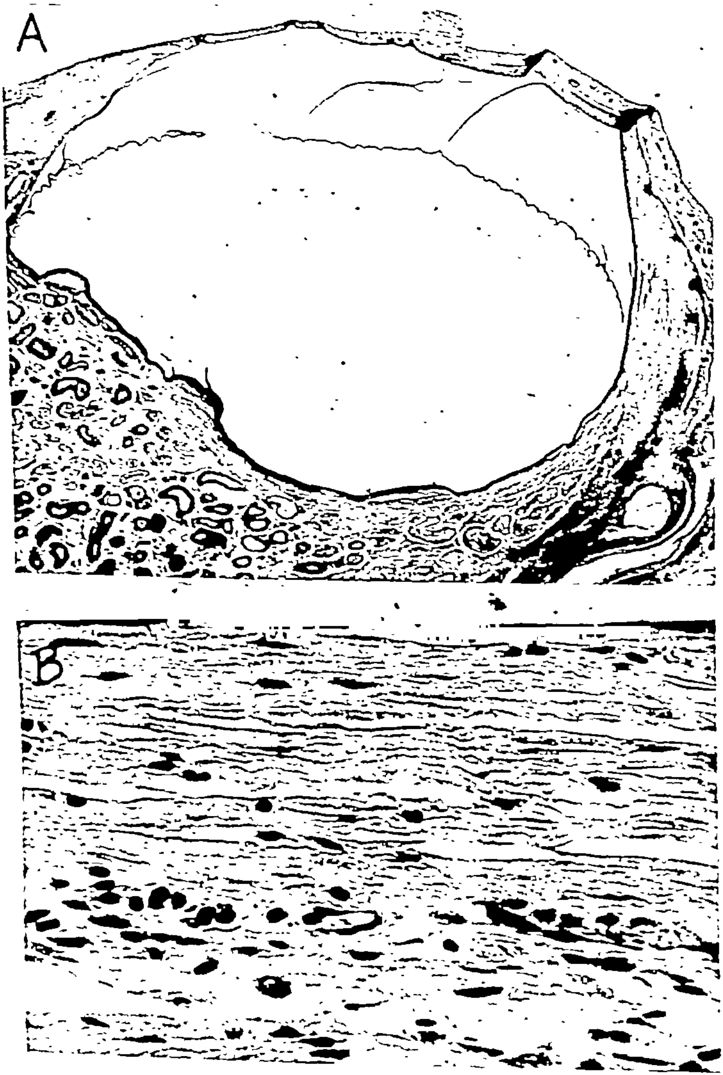

Fig. 2

Pathological diagnosis (Dr. D. C. McGoon): "Testis: Cysts of tunica albuginea."

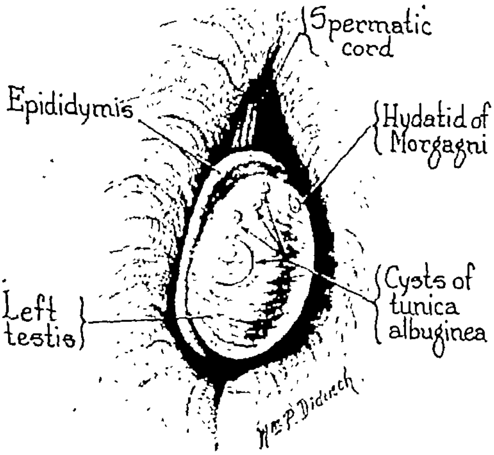

FIG. 3

DISCUSSION

Academic interest prompts us to speculate on the causative agent or factors responsible for the production of cysts of the tunica albuginea testis. It is of academic interest because, regardless of the etiology, all nodules in or on the testis should be surgically explored to rule out neoplasm.

There are three general categories that should be considered as potential causative factors in this disease. They are: 1) congenital anomaly, 2) trauma, and 3) infection.

The first category is difficult to evaluate from the pathological material in our hands. Perhaps a study of the tunica albuginea testis of many fetuses or newborns might throw some light on this phase of the problem. Studies applicable to this problem are not known to be in the literature.

Trauma, it appears, would contribute little to the causation of these lesions since in none of the cases was any history of trauma to the genitalia given. The last two cases reported here were closely questioned in this regard by the author. There was no evidence of previous hemorrhage noted on our histological studies.

The importance of previous infection in causing these lesions may be evaluated in this study, in two ways: 1) histological study of the tissue removed at surgical exploration; and 2) physical characteristics of the adjacent structures such as vasa and epididymides, prostate, and opposite testis.

A restudy of the microscopic sections revealed that there was evidence of chronic inflammation with round cell infiltration and fibroblastic proliferation in tissues from cases 1 and 2, as shown in figs. 1 and 2, *A*. In case 3 the small amount of tissue removed revealed no inflammatory reaction.

Physical examination revealed some evidence of a previously existing inflammatory process in cases 2 and 3. This was characterized by thickening and induration of the vas and epididymis of the same side as the involved testis, or the opposite one as in case 3.

From this study it appears that the cystic lesions of the tunica albuginea are commonly associated with an inflammatory reaction in the testes or adjacent structures. It is not unreasonable to conclude that there may be a causal relationship between cysts and infection or inflammation. The other factors discussed, i.e., trauma and congenital anomaly, seem negligible in their contribution to the causation of this lesion. However, further study on vascular or lymphatic anomalies may be illuminating.

SUMMARY

Three cases of cysts of the tunica albuginea testis are presented and the rarity of the condition is pointed out. Etiological factors are discussed in the light of material available to us for study.

It is concluded that since there was evidence of inflammation in either testis, epididymis or vas in all cases, previous infection may well play an important part in the formation of cysts of the tunica albuginea testis.

I wish to thank Mr. William P. Didusch for the drawing which so clearly depicts the condition found at operation.

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BANTHINE IN UROLOGIC DISORDERS

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Banthine is a quaternary ammonium salt with an anticholinergic effect acting in clinical doses on the parasympathetic autonomic ganglia and blocking the action of acetylcholine at the postganglionic nerve endings. In larger doses it blocks transmission through all the autonomic ganglia and in still larger doses it has a curare-like effect. It has been used clinically for the past few years with good results in the treatment of peptic ulcer. One of its side effects is bladder wall relaxation causing urinary retention which has been quite marked in cases of obstruction of the bladder neck. The occurrence of urinary retention has led the author to the use of banthine in cases associated with urgency and increased frequency of micturition.

The detrusor muscle of the bladder is innervated by the parasympathetic fibers arising from the first to the fourth sacral spinal segments. These fibers are conveyed to the bladder in the pelvic nerves and connect with the ganglion cells lying in close relation to the bladder wall. Centers for micturition lie in the midbrain, hind brain and spinal cord. There is also a center in the premotor cortex and local reflex arcs occur in the bladder wall. Conceivably banthine will exert its anticholinergic effect on the bladder as it does elsewhere in the body. This would result in the opposite effect of doryl, urecholine and mecholyl.

In a urologic practice many patients are seen, especially women, who complain bitterly of frequency and urgency associated with a small capacity of the bladder. Examination of these patients may reveal chronic trigonitis the cause of which cannot be determined, or frequently nothing is found in the bladder. Despite the use of all known medications the symptoms continue unabated. Frequently these cases are due to severe emotional states which lead to the vicious cycle of frequency, urgency and decreased capacity of the bladder. If, in these cases, the efferent stimuli to the bladder could be blocked or depressed the vicious cycle would be broken and the symptoms would decrease or disappear. Because of the above reasons and the relative safety of banthine, the author decided to use it in the types of cases described below.

HUNNER'S ULCER

Case 1. F., aged 50, gross hematuria 1947, cystotomy and fulguration of a bleeding ulcer without relief. Hunner's ulcer diagnosed 1947. No healing with any form of medication, frequent attacks of pyelonephritis necessitating prolonged hospitalization. Morphine addiction occurred because of severe pain. While preparations were being made for a bilateral ureteral transplant, banthine was given September 1950, 100 mg. q.i.d. In a few days, symptoms considerably relieved and patient was able to get out of bed. In 1 month patient able to work and continued to take banthine for 6 more months without any other type of therapy. Five months ago patient discontinued banthine and has taken no medication. Cystoscopy September 10, 1951: bladder capacity 300 cc., bladder wall normal in appearance with avascular area at site of previous ulcer. Patient believes she is cured and does not require treatment. A detailed discussion of this case will be published later.

Case 2. F., aged 62, Hunner's ulcer 3 years duration. Previous treatment of no avail; banthine started February 1951, marked relief of symptoms. Symptoms aggravated with discontinuance of banthine; emotional strain requires increased dose of banthine.

Case 3. F., aged 32, Hunner's ulcer 6 weeks' duration, chronic cystitis 2 years. Banthine started with almost complete relief of symptoms. Cystoscopy 1 month after therapy revealed ulcer still present but smaller in area.

TRIGONAL CYSTITIS

This is an inflammation of the trigone of the bladder characterized by a greatly increased vascularization of the trigone or edema of the trigone which usually decreases towards the ureteral orifices; the edematous area may be dull red but more often of a greyish hue. This condition is more frequent in women than men and is usually associated with severe emotional states. Seven cases, five women and two men, have been treated with banthine with great alleviation of symptoms. Other drugs had very little effect. One man, aged 43, had frequency day and night of 18 years duration, urinating 24 to 30 times per day. After taking banthine for 1 week the frequency has been decreased 50 per cent and his bladder capacity doubled.

PROSTATECTOMY

Occasionally in very nervous patients after prostatectomy, suprapubic or transurethral, urgency with a decreased capacity of the bladder is a serious problem. It is true that in most of these cases the symptoms disappear with healing of the posterior urethra. However, in two such cases banthine was of considerable benefit during the period of healing.

CONCLUSION

Banthine has been used with benefit in 12 cases of disturbed micturition associated with frequency, urgency and decreased capacity of the bladder. Twelve cases are insufficient to warrant any definite conclusion. However, it is hoped that others will use banthine in urological conditions to evaluate its effectiveness, and further investigative work is in progress.

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HUMAN SERUM ALBUMIN FOR ANURIA

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An abdominoperineal resection of the colon was performed on January 17, 1951, under endotracheal cyclopropane. The patient was returned to the operating room that night because of continued bleeding, and the perineal wound was packed, again under endotracheal cyclopropane anesthesia. As the blood loss had been extremely large during each procedure, and inevitably accompanied by hypotension, particularly during the first operation, I was naturally concerned for his postoperative urinary output. I was pleasantly surprised to be told the next morning that it was 2200 cc. This was considerably more than I had ever seen, regardless of the extent of administration of blood, plasma, or electrolytes; in thinking over the case, I discovered that the only new medication used in this case was human serum albumin, of which he received 100 cc (25 gm.) during the first operation. He was given 2500 cc of blood during the resection, and an additional 1500 cc during the packing of the perineal wound, in addition to several transfusions between the two operations.

Excision of a ruptured intervertebral disk and spinal fusion were performed on October 25, 1951 under spinal block supplemented with pentothal anesthesia. Bleeding did not appear to be excessive during the operation and the patient was given 1000 cc of blood. He went into shock during the first postoperative night and 500 cc (125 gm.) of human serum albumin were administered; his condition was good in the morning. His urinary output for each of the first four postoperative days was reported as 5150 cc (an emesis of 700 cc may or may not have been included in the output), 2400 cc, 4000 cc, and 1850 cc.

An abdominoperineal colectomy was done on November 6, 1951 under endotracheal ether anesthesia. Cyclopropane was first used but was discontinued when the surgeon insisted on using epinephrine later in the operation. The bottle to which an indwelling urethral catheter was connected was emptied on adopting the lithotomy position; it contained only 40 cc at the time, after 4 hours of anesthesia. One hour and 50 minutes later there was still no urine in the bottle and the bladder was felt by one of the surgeons to be empty. The effect of serum albumin in stimulating urine formation in the two preceding cases was recalled, and it was immediately administered. Urine appeared in the bottle 30 minutes later, when 85 cc (21.25 gm.) had run in. The question arises as to any connection between the use of epinephrine and urinary suppression, as by provoking spasm of the renal vessels or of the ureters. The anuria was not due to shock. There was

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

no hypotension during the operation; the albumin was given solely to initiate urine formation. His urinary output for the first postoperative day was 3050 cc.

It is believed that human serum albumin possesses a specific effect in stimulating urine formation. It is suggested that it be administered as a treatment for anuria, and it is further recommended that 50 or 100 cc of serum albumin be given prophylactically during long operations, particularly in those accompanied by hypotension or severe bleeding.

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PROSTATIC AND PERIPROSTATIC PHLEBOGRAPHY

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Our interest in the anatomy of the periprostatic veins was stimulated by the recent excellent contribution of Beneventi in which the vessels of the prostate of necropsy specimens were injected with a plastic solution and anatomical studies made. Our own experience with the retropubic approach to the prostate and vesical neck often led us into a plethora of venous channels uncharted in the usual anatomical text books. The desirability of demonstrating these vessels before encountering them on the operating table was readily apparent and to this end, a technique of prostatic or periprostatic phlebography was evolved.

A perusal of the literature reveals that very little has been contributed to this subject since Santorini described these veins in his original anatomical studies in 1724. No accurate description was given nor was any attempt made to discuss the multiple variations encountered. He merely stated that a plexus of veins covered the surface of the prostate and bladder.

The current anatomy texts describe the prostatic plexus as lying on the fibrous true prostatic capsule and beneath the endopelvic fascia. This prostatic plexus communicates with a plexus about the vesical neck and around the seminal vesicles and empties laterally into the internal iliac veins. The deep dorsal vein of the penis drains into this periprostatic plexus. This latter fact was the important clue in the development of the technique by which the veins of the prostate could be demonstrated.

Bumpus (1934) and Flocks (1937) delineated accurately the arterial distribution to the prostate and the changes incident to hyperplasia of the prostate, prostatic malignancy and in the postoperative gland. It is accepted that the prostate receives arterial blood from the inferior vesical artery penetrating the capsule at the prostatovesical junction and dividing into branches which extend deeply the peri-urethral glandular areas and superficially along the postero-lateral margin to supply the greater mass of true lobar prostatic tissue and the area contiguous with the verumontanum.

Bumpus and Antopol (1934) produced several injection-specimens which outlined the normal pattern of three main arterial planes. The first was a longitudinal plexus of arteries just beneath the capsule of the gland. The second plexus ran roughly perpendicular to the first and penetrated prostatic tissue to a third system running longitudinally again and lying just beneath the mucosa of the prostatic urethra. They demonstrated clearly the increase in number and tortuosity indicative of possible arteriosclerotic changes in the aging and hypertrophying gland.

Crabtree (1947) reported venous invasion following urethrography and presented two films of phlebograms resulting from injection of the radiopaque media in both the superficial and deep veins of the penis. These experiments were

Read at annual meeting, Mid-Atlantic Section, Philadelphia, Pa., April 17, 1952.

arried out on cadavers. In their x-rays, the prostatic plexus was not well outined although the veins of the pelvis, both superficial and deep, were clearly isualized. Crabtree also presented urethrograms with venous reflux but did not utilize phlebography *per se.*

The first successful radiographic demonstration of the periprostatic and deep pelvic veins in vivo was performed in 1950 by Ceccarelli who injected an iodine preparation and obtained phlebograms of the pelvic vessels. We were not aware of this contribution when the present study was started.

The main objectives of our study were: 1) adoption of a simple and safe technique; 2) development of a reliable radiographic procedure; 3) accurate interpretation of the findings.

Towards the first end, we experimented with various sized cannulae, needles and catheters utilizing our trials and previous experience with retrograde aortography. The following procedure has been adopted and employed with uniformly good results:

Materials required are A) No. 20 needle 1½ inches in length, B) Two glass syringes with Luer-Loks (20 cc), C) 3-way stopcock, D) 500 cc intravenous saline and tubing, E) Tourniquet, F) 25 cc of a 70 per cent solution of one of the organic iodine preparations.*

The penis is prepared with a tourniquet about its base for a few minutes and the skin cleaned as for venipuncture. A No. 20 needle is inserted into the deep dorsal vein of the penis by percutaneous puncture. As can be seen from anatomical studies, the deep dorsal vein of the penis is, in most cases, an invariable sturcture while the superficial dorsal vein or veins present a most varied arrangement. The distended veins on the surface of the penis may be present as two parallel dorsal structures, two laterally placed veins, or one or both may be absent. The deep dorsal will become distended when a tourniquet is placed about the base of the penis and is discernable as a midline swelling passing from the mid shaft to the region of the suspensory ligament. Depending on the amount of subcutaneous fat, this vein may be seen as a blue tubular structure beneath the skin.

Having produced distention of the deep dorsal vein, the penis is placed on the stretch. This will delineate it vividly and venipuncture may then be accomplished.

Failure to enter this vein will produce a subcutaneous infiltration of the dye which may be dispersed by the injection of 1500 units of hyaluronidase into the area. If a superficial vein is entered, the dye will not pass beneath the pubis to fill the periprostatic plexuses but will instead demonstrate the superficial fe filling injec and pudenal veins.

A 3-way stopcock is connected to the needle and one limb is connected to a bottle of intravenous fluid and the other limb to a 20 cc syringe.

Once entry into the vein has been accomplished, the syringe is disconnected, the needle taped in place and the intravenous saline solution is allowed to flow.

Ten cubic centimeters of a solution of urokon 70 per cent is then injected via a Luer-Lok syringe through the stopcock and into the dorsal vein (fig. 1).

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*We are indebted to the Mallinkrodt Chemical Works, St. Louis, Mo., for a most liberal supply of 70 per cent urokon to carry out this study.

The radiographic technique consists of taking a film at 90–94 KV and 200 MA at 1/10 or 1/5 a second with the x-ray tube coned down at 42 inches and angled 5 degrees towards the patient's head. Stereoscopic films are taken, the first after 5 cc of urokon has been injected and the second film as the last 5 cc of dye is being injected. The injection of the dye is made at maximum rate throughout and films are taken with the patient holding his breath and bearing down as in defecation. The injection is concomitant with the venous flow towards the vena cava.

The patients have not complained of any marked discomfort from either the venipuncture or the injection. Occasionally, the dorsal vein is difficult to enter, but we were surprised as to the ease with which venipuncture was performed in most cases, size of the organ not withstanding. At first, we were loath to inject such a large concentration of dye intravenously realizing than an allergen of this nature is more dangerous in the venous circulation than in the arterial as in aortography. However, our initial timidity was unwarranted as we have employed this procedure in patients with asthmatic and allergic histories with no ill effect. The most pronounced reaction is one of local heat and occasionally a transitory period of respiratory oppression lasting a few seconds. To this end, it is well to have available an emergency kit of intravenous benadryl, adrenalin, coramine and aminophylline.

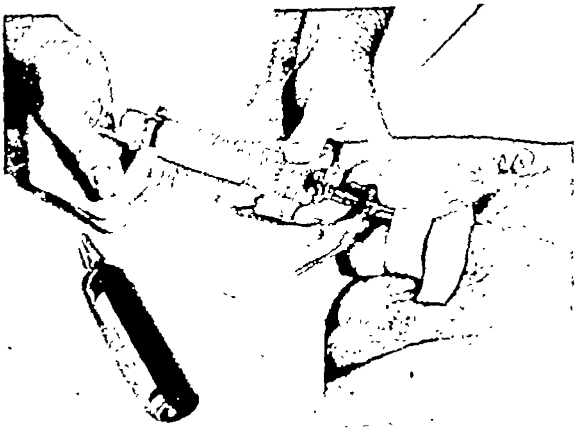

Fig. 1. Technique of injection

At the onset of the study, a single film technique was employed, but the present method of taking two stereoscopic films was found to be more informative. After plexus [illegible], the stopcock is switched back to the intravenous saline and about 100 cc is allowed to run. Thus, if additional films are desired or if the ones being developed prove to be unsatisfactory, it is only necessary to switch the stopcock back to its injecting limb and repeat the procedure. At the termination of procedure, the needle is withdrawn and gentle pressure applied for a few seconds. All bleeding stops readily. Occasionally, there is some discoloration of the penis for several days. In one of the first cases, a superficial sluff occurred while experimenting with catheterization of the vein with small polyethylene tubing as in retrograde aortography. This sluff was due to extravasation of the dye into the subcutaneous tissue, but healed quickly without scarring.

The interpretation of the results was the most difficult part of the entire procedure. It entailed a consideration of 1) the normal anatomy of the prostatic, periprostatic and deep pelvic veins; 2) delineation of the venous pattern about the prostate as might be encountered in retropubic surgery; 3) difference in venous distribution in cases with a normal prostate gland, benign hypertrophy, and malignancy; 4) the effect of surgery on these venous channels; 5) the effect of mechanical or infectious obstruction on these venous channels.

By accident more than intent, we have observed clear outlining of the upper femoral, internal and external iliac, and obturator veins as well as the lower vena cava.

In analyzing our series of cases only the most striking examples will be presented.

In vivo, the deep dorsal vein of the penis empties directly into a liberal plexus or network of veins which communicate freely with each other and then delineate to form the lateral prostatic plexuses lying on the dorso-lateral margins of the prostate superficial to the fibrous capsule. These veins, in turn, empty into the internal iliac veins communicating with the obturator veins, the vesical plexus and the plexuses on the anterior surface of the rectum. From the retrograde injection, it appears that there are no valves in these deep pelvic veins and consequently, the external iliac and upper femoral veins as well as the lower vena cava were often demonstrated. This technique has been employed to delineate the vascular supply to the anterior surface of the prostate in patients who were scheduled to undergo a retropubic prostatectomy and on the strength of this radiographic procedure, it was simple to transfix the superficial fibrous capsule in the areas where a rich vascular network was found. This step reduced considerably the blood loss usually encountered in the retropubic approach.

The findings encountered in a young man, age 28, are illustrated in figure 2. The general pattern is the same. A rich network of vessels course over the prostate but they are almost contiguous indicating a small normal prostate gland. The typical picture of a benign hypertrophy of the prostate is indicated in figure 3. This reveals an increase in vascularity both in quantity of veins and area covered by this distended venous pool. The lateral plexuses are widely separated and give the impression of a mass enlarging the area between them. This is even more striking when our films are viewed in stereo.

The findings in a case of carcinoma of the prostate diagnosed by rectal palpation are illustrated in figure 4. This diagnosis was later confirmed by biopsy. The relative paucity of vessels, the lack of distention and areas of irregular filling are very striking. This phenomenon has been attributed to the thrombosis of veins and is very suggestive of malignancy. Ceccarelli also observed this finding in carcinoma of the prostate gland. This technique of phlebography may be employed as an aid in the diagnosis of occult or suspected carcinoma and allows an early diagnosis where there is suspicion of malignancy.

It was noted that the injections not only demonstrated the periprostatic veins but also filled the deep pelvic veins, and it was believed that this procedure might be employed to demonstrate occlusive clots in patients presenting symptoms of possible thrombophlebitis. Phlebography performed on a patient who was suspected of having a thrombophlebitis of his left leg revealed an irregularity and filling defect in the left femoral vein (fig. 5). At operation, a large clot was aspirated from the femoral vein from an incision in the superficial femoral vein.

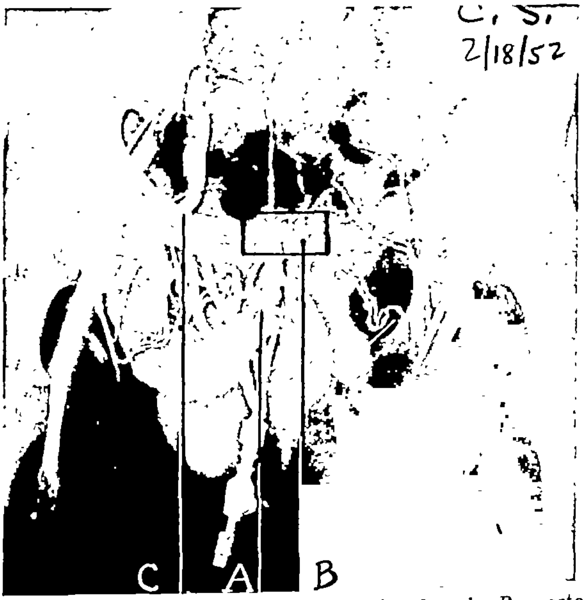

FIG. 2. Normal 28 year old man. *A*, deep dorsal vein of penis. *B*, prostatic plexus. *C*, internal iliac vein.

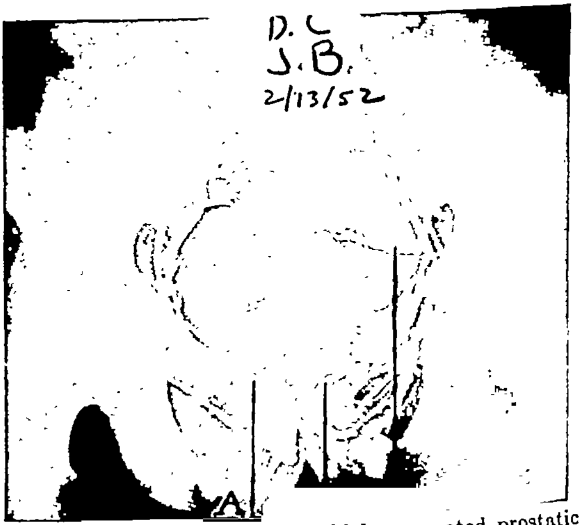

FIG. 3. Benign prostatic hypertrophy. *A*, widely separated prostatic plexus with increased vascularity. *B*, anastomosis with inferior hemorrhoidal vein.

A further consideration of this phenomenon will lead us to use this method of phlebography in the diagnosis of various occlusive diseases of the pelvic veins.

In cases of priapism, it may be used to demonstrate location of thrombosis in the dorsal vein or deeper veins and thus provide accurate information concerning the underlying pathological process and enable the examiner to determine the proper type of therapy.

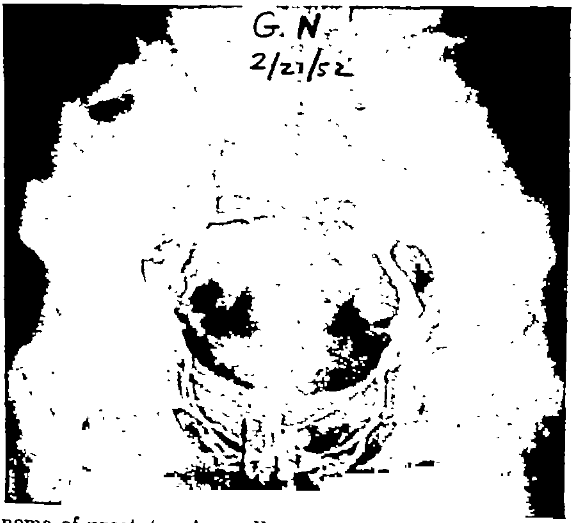

FIG. 4. Carcinoma of prostate. *A*, small prostatic plexus. *B*, note paucity of veins and numerous thromboses.

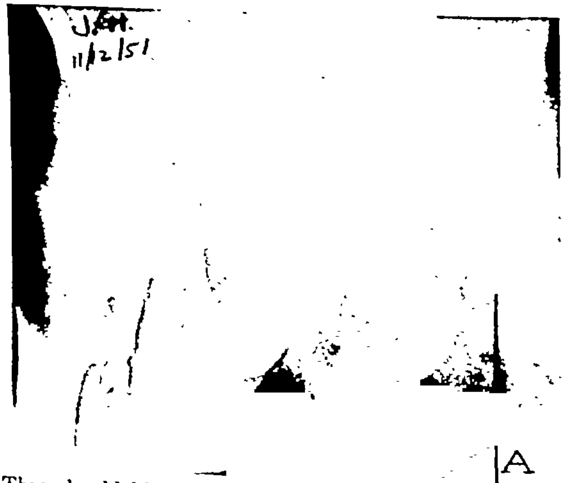

FIG. 5. Thrombophlebitis of left leg with thrombus in left femoral vein, *A*.

This technique may prove of value in the diagnosis of all types of pelvic tumors such as carcinoma of the sigmoid-rectum, carcinoma of the bladder and retroperitoneal tumors of the Hodgkins and lymphosarcoma group. It would also be interesting to observe what changes in venous pattern may incur upon tuberculosis of the prostate and seminal vesicles.

CONCLUSIONS

Phlebography is a simple, and safe, means of delineating the veins of the periprostatic regions and the pelvis. It is helpful in diagnosisng prostatic enlargement, in the differentiation between benign and malignant disease of the gland, and in outlining the size of such enlargement. Phlebography provides accurate information concerning the venous distribution over the anterior surface of the prostate as encountered in retropubic surgery. Finally, it may well be a significant aid in the diagnosis of thrombophlebitis of the femoral and iliac veins and other diseases involving the pelvic veins.

We are fully cognizant of the danger of drawing conclusions from a small series of cases, but feel certain that further experience will prove that prostatic phlebography is another adjuvant in the growing urological diagnostic armamentarium.

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PELVIOPROSTATIC VENOGRAPHY: PRELIMINARY REPORT

RAYMOND J. FITZPATRICK AND LOUIS M. ORR

In reviewing pertinent literature on the vascular supply of the prostate gland, the question presented itself of the possible value of outlining the venous pattern of this organ by the injection of radio-opaque material into the deep dorsal vein of the penis. The deep dorsal vein, after it passes through the two parts of the suspensory ligament and through an aperture formed by the arcuate pubic ligament and the transverse ligament of the pelvis, divides into two branches which enter the pudendal plexus. The pudendal plexus in turn communicates with the vesical plexus and the internal pudendal vein and drains into the vesical and hypogastric vein. The deep dorsal vein also communicates below the symphysis pubis with the internal pudendal vein.

Batson, in his work on the relationship of the vertebral veins and their role in the spread of metastases, injected into the deep dorsal vein of the human cadaver and also the anesthetized rhesus monkey artist's tube water color and was able fluoroscopically to determine the vascular communications between the pelvic structures and the vertebral column. Beneventi and Noback studied the distribution of the blood vessels of the prostate gland and urinary bladder by dissecting the pelves of several cadavers following the injection, under gentle pressure, of the deep dorsal vein of the penis with freshly mixed and heated vinylite solution.

In a review of American literature on the subject of venography, no reports could be found of the injection of radio-opaque materials into the deep dorsal vein in the living subjects, which prompted the investigation of its possible value in clinical cases. A preliminary report of the results of five such injections is herewith presented.

TECHNIQUE

After some trial and error the following technique has been found most suitable. The patient is prepared and draped in the usual manner. A small gauze sponge is placed about the base of the penis, over which a small tourniquet is then secured. Under local novacaine anesthesia a transverse incision is made in the midshaft of the dorsum of the penis and dissection carried down until the deep dorsal vein is identified beneath Buck's fascia. A small V-shaped nick is made in the dorsal wall of the vein and a polyvinyl tube No. 442-T (B-D plastic tubing) is inserted for a distance of some 5 to 7 cm. or more, depending upon the relative location of the penile midshaft. After the tubing is inserted, Buck's fascia and skin are closed with interrupted sutures of 00 plain catgut with the polyvinyl tube protruding from the center of the incision. The wound is closed before any x-ray films are made and while the anesthetic effect is still present. A scout film of the lower abdomen is then made. When an urethral catheter was already in place for various clinical reasons, the bulb of the Foley bag catheter was filled with diodrast to reveal its relative position to the vesical neck. The venogram is made by injecting 10 to 15 cc of 35 per cent diodrast as rapidly as possible and the exposure is made just as the last 1 to 2 cc of the solution is being injected. For the purpose of injection it has been found that a 20 cc syringe, using an ureteral catheter adapter to connect syringe to tubing, has been quite satisfactory. The insertion of a large bore needle into the lumen of the tubing very definitely diminishes the speed with which the material may be injected. The advantage of the plastic tubing lies in the fact that the blood does not clot in the tubing between film exposures. Leakage of blood from the tubing can be prevented by placing over the end of the tubing an ureteral catheter adapter, one end of which is blind. Lateral or oblique films can be made if desired in the manner above described. In some cases, abdominal compression, as well as tourniquets on both thighs, was carried out in order to slow down venous return. This procedure was discontinued in order to achieve the utmost simplification of technique and because it was believed that it added little to the actual outlining of the pelvioprostatic venous pattern. It is interesting to note that Anderson, in his study, in which he injected diodrast into the femoral vein, revealed that abdominal compression resulted in shunting of blood into the vertebral venous system.

By utilizing polyvinyl tubing, one need not be concerned about clot formation in the lumen and thus several exposures can be made. If desired, the remainder of the usual 20 to 30 cc of 35 per cent diodrast solution may be injected and routine excretory urograms may be made. At the conclusion of the exposures the polyvinyl tube is withdrawn and pressure made over the opening in the vein for a few moments. This is usually sufficient to secure adequate hemostatis. A firm dressing is then applied. The entire procedure is very well tolerated and no postoperative distress has been experienced to date.

CASE REPORTS

The following 5 patients were subjected to the aforementioned procedure, or modification thereof. A very brief clinical history and the accompanying roentgenogram is presented in each case.

Case 1. (C.W.H.) hospital No. 99124, a 75 year old white man, was admitted to the Orange Memorial Hospital on December 20, 1951, for a penile amputation for epidermoid carcinoma, grade 4. Surgery was performed the following day, at which time a polyvinyl tube was inserted into the deep dorsal vein of the penis and the pelvio-prostatic venograms performed. Figure 1, *A* demonstrates an essentially normal pelvioprostatic pattern.

Case 2. (J.F.B.), hospital No. 97997, a 60 year old Negro, entered Orange Memorial Hospital on November 27, 1951. On November 28, a penile amputation and bilateral inguinal node dissection was performed for a squamous carcinoma of the penis, grade 3, with metastases to the inguinal lymph nodes. A polyvinyl tube was inserted into the deep dorsal vein at the time of surgery and the patient taken to x-ray immediately for a pelvioprostatic venogram. The results are shown in figure 1, *B* and an essentially normal pelvioprostatic venogram is seen.

Case 3. (C.S.), hospital No. 97623, a 47 year old Negro, was admitted to Orange Memorial Hospital on November 19, 1951 complaining of a mass in the right groin. He had noted intermittent hematuria over a period of several months. Cystoscopic examination revealed the entire bladder to be involved by a very extensive carcinoma and bimanual examination under anesthesia revealed a suprapubic mass the size of a large grapefruit. Biopsy of the groin and bladder revealed an epidermoid carcinoma, grade 4. Pelvioprostatic venography was performed on November 26 and the findings are depicted in figure 1. *C.* Note the absence of the normal venous pattern in the prostaticovesical region, which is thought to be undoubtedly due to the extensive involvement of the entire pelvis by the carcinoma. This patient went downhill rapidly and died on December 7, 1951.

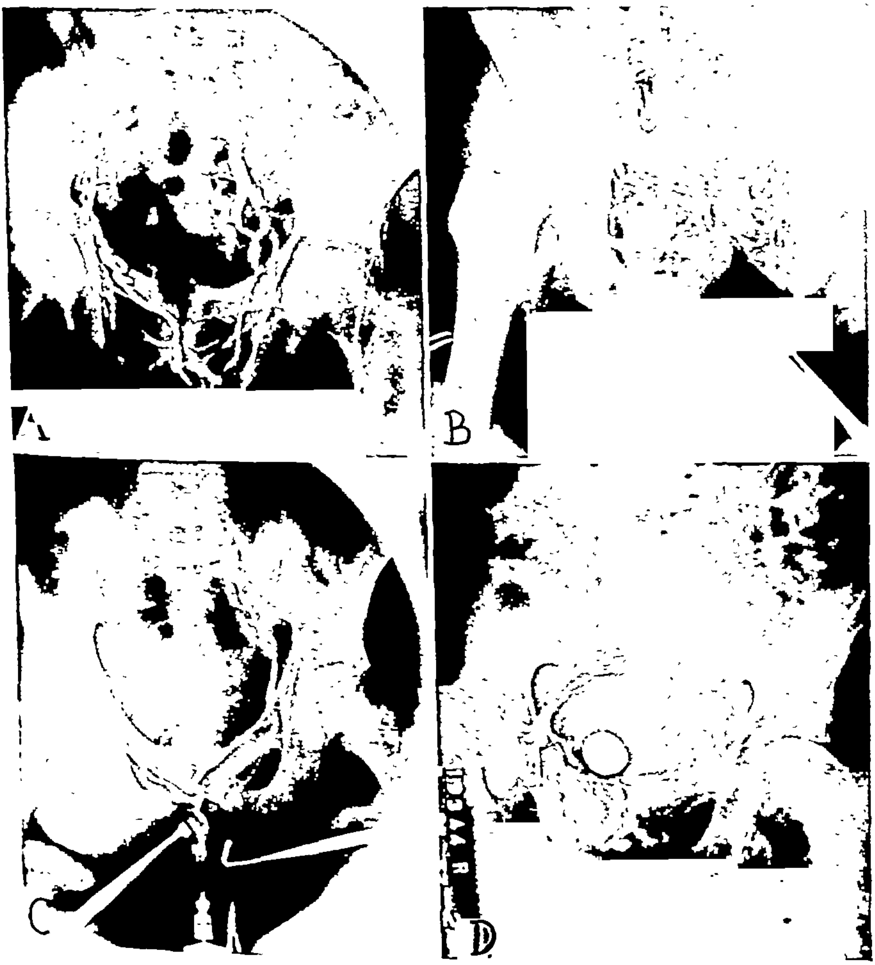

FIG. 1

Case 4. (E.W.M.), hospital No. 103705, a 72 year old retired physician, was admitted to Orange Memorial Hospital on March 13, 1951 for investigation of a large mass in the left suprapubic area, which on bimanual examination was the size of a large orange. On rectal examination the mass extended upward beyond the reach of the finger from the upper aspect of the left lateral lobe of the prostate and extended also medially beyond the midline and laterally to the left. It was nontender and quite firm in character. Approximately 5 to 6 months previously a biopsy of a mass in the right lower quadrant had revealed an adenocarcinoma, grade 2. From communication with the physician's surgeon at that time it was learned that the mass was retroperitoneal and on pathological examination by the local pathologist, and also by Dr. A. P. Stout of Columbia University, the origin of the tumor was considered to be possibly from a seminal vesicle. A cystoscopic examination was attempted but was impossible because of the size of the mass, which precluded the entrance of the cystoscope. A pelvioprostatic venogram was performed on March 26, and the unusual findings are depicted in figure 1, *D*. Note the manner in which many of the vessels have been pushed laterally and note the apparent compression and small size of the vessels on the left. Also note the anastomotic connection extending from the right and crossing over the superior aspect of the tumor to communicate on the left. Reflux is also observed down the left femoral vein, which may be due to compression of the venous return on that side. The collection of contrast medium on the right occurred with the first injection. The tubing was slightly withdrawn and other exposures made. Because of other complicating factors surgical exploration has had to be deferred until a later date.

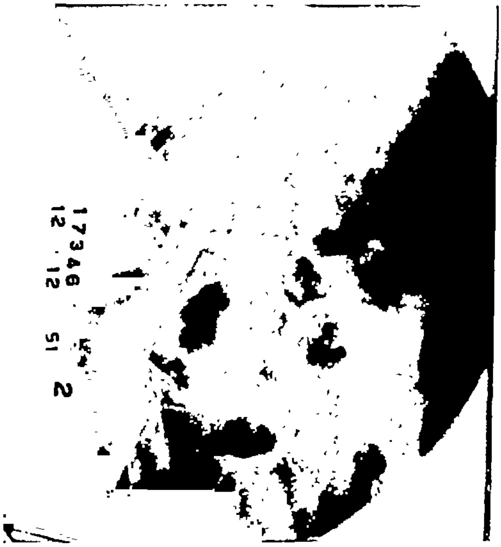

FIG. 2

Case 5. (E.T.), hospital No. 96982, a 58 year old Negro, was admitted to Orange Memorial Hospital on November 5, 1951 because of severe urethral strictures and "watering pot" perineum. A pelvioprostatic venogram was performed December 12, according to the technique described (fig. 2). This was unsatisfactory because the tubing had been inserted too far. The dye is passing apparently by the external pudendal vessels into the greater saphenous vein, which in turn is communicating with the femoral vein. Another exposure was contemplated but on attempting to partially withdraw the tubing the patient decided to turn on his side with the result that the entire tube was withdrawn.

CONCLUSIONS

Five cases in which pelvioprostatic venograms were done in the living patient are presented. These studies were made in an attempt to evaluate the usefulness of the procedure from the clinical standpoint. A search of available American literature would indicate that this study is the first of its kind done in the living human. It is difficult to be certain at the present time of the value of this procedure from the standpoint of adding further information to our diagnostic armamentarium. However, until a sufficiently large number of pelvioprostatic venograms are performed, one must reserve judgment as to its value. Until a sufficiently large number of normal patterns are ascertained the departures from normal cannot be appreciated. In future studies it will be interesting to learn whether there is any change of pattern of the vessels in cases of prostatic carcinoma with extension beyond the capsule. Other uses of the procedure immediately suggest themselves and they will be made the subject of a future, more complete report.

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MINERAL OIL EMBOLISM—REPORT OF A CASE

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It is considered worthwhile to present the case report of a young man who succumbed to massive mineral oil embolism. This complication with its fatal outcome on this occasion occurred as a result of the instillation of mineral oil under moderate pressure into the urethra, as an aid to the passage of a catheter. This treatment in the course of manipulative efforts to pass a urethral catheter was that used many times previously without trouble and has been suggested and prescribed as a routine method by clinics since before the turn of the century (Thompson), and as recently as 1928 (Crance).

After the death of this patient the autopsy findings revealed the true cause of his death. A search of the literature was then made to ascertain the frequency of this tragic complication. Much was found in the study with regard to fat embolism, but only two articles (Carr and Johnson; Patterson) reporting a total of 3 cases, dealt with mineral oil embolism as a result of urethral instillation of oil. Because of the rarity of this complication it was thought that the addition of our case report was indicated. It was believed, however, that the rarity of this complication was not a true one and that in the past deaths have occurred many times due to oil embolism. The deaths, if they have occurred, have been attributed to other causes and have gone unrecognized,—or, that if recognized, reticence to report the case has been responsible for the paucity of findings in the literature.

Fat embolism, of which mineral oil embolism could be considered a subgroup, has received much investigation in the past and yet many of the phenomena associated with fat embolism are still not explained.

As far back as 1669, milk was injected into animals producing fat embolism. Magendie produced the same effect by injecting olive oil intravenously in 1827. Of course, it was not recognized as such at the time and Magendie felt that he had caused an increased viscosity of the blood resulting in capillary damage and hemorrhage. This supported his hypothesis of the time, that increased viscosity of the blood in fevers and sweating led to capillary occlusion and pneumonia.

Zenker in 1862 described the first case of traumatic fat embolism and in the same year Virchow repeated Magendie's experiments and demonstrated fat embolism, finding the emboli not only in the lung but also in the liver and kidney and their capillaries. In 1863, Bergman demonstrated experimentally most of what is known today:

1) Fat embolism is a serious complication which may lead to death through pulmonary edema and cardiac paralysis.

2) Rupture of the pulmonary capillaries is possible and gives rise to the appearance of fat in the alveolar spaces.

3) The fat is not fixed in the blood stream or the vessel lumina and part of it may pass through the vessel wall and appear in the tissues.

4) A small portion of the fat passes through the lung capillaries and appears as emboli in the kidney and spleen.

It was not until 1873 that Von Bergman diagnosed the condition clinically. Previous to this, however, many cases had been recorded at autopsy. In 1877 Riedel felt that there was some degree of fat embolism in every case of fracture, a feeling that is entertained by some observers even today.

Characteristically, in fat embolism, there is history of bony trauma, followed after an interval by signs and symptoms that in retrospect alone, are very easy to evaluate. There is described an interval of usually 2–3 days before signs and symptoms develop but the impression is gathered from the literature that the onset of symptoms is governed by the degree of embolism and biochemical circumstance. This free interval is not described in experimental work and is not stressed in the literature of recent date.

Fat in the globular form, larger than 4 microns in diameter, plug the pulmonary capillaries. This leads to cyanosis, an acceleration of the pulse, varying effects on the blood pressure, and in severe cases, dilatation of the neck veins. The right heart is dilated, the left empty. Some emboli squeeze through the capillaries of the lungs and proceed everywhere, brain, spinal cord, myocardium, liver, kidneys, muscles and skin. In the latter site, petechiae are observed usually over the chest and neck. They have been described as appearing earliest in the conjunctiva. These hemorrhages in the skin, so characteristic, unfortunately have been recorded in only 15 per cent of the cases. These emboli may in turn get through the peripheral system of capillaries and re-embolize the lung. This may take 3–4 days. This sequence of events may be repeated 2–3 times giving the cyclic effect. The mortality of fat embolism varies markedly in the different reports, anywhere from 50 to 90 per cent but it is of considerable interest that there is continual repetition of the statement that the diagnosis first comes to light almost without exception in the autopsy room. It is relatively easy, once one's attention is forcibly focused on a subject like fat embolism, to interpret other unusual experiences along this line correctly. This undoubtedly accounts for the variance in the mortality figures.

Fat embolism occurs when globules larger than 4 microns in diameter are absorbed into the venous channels. This implies mobilization of the fat from fat cells, under pressure and in situations where veins are open. This set of circumstances is most often provided in fracture. This theorizing fails to account for the occurrence of fat embolism in other circumstances such as operations other than on bone, etc. The argument as to the source of the embolic fat, whether it is from the fat depots in tissues or from the blood, remains unsettled, but it is agreed that there is no correlation between the amount of fat and the effect.

It is known that the lethal dose of fatty acids, particularly oleic, is only one-tenth that of neutral fats. Oleic acid does not appear in the composition of bone marrow fat until the age of 15, which explains the absence of fat embolism in children.

Fat embolism can complicate nearly every known disease, infection or poison. Taking their cue from these observations it has been found experimentally that certain toxins induce fat embolism. It has been learned that heparin can change the physical state of the blood fat, so possibly proceeding along this line of inquiry, it will be demonstrated in the not too distant future whether or not the blood or tissue fat has been the donor in fat embolism. It is more than possible that either, on occasion, can be the source and it may just be that under certain conditions both sources may be utilized. It is also interesting to note that there have been no reports on blood fat studies either before or after the embolism. This must be of some significance for, whereas, a 70 kilo man is supposed to survive an intravenous dose of 120 cc of oil as deduced from animal experiments (Lehman and Moore), yet those same experiments revealed that during an alimentary lipemia the lethal dose was possibly $\frac{1}{6}$ of the accepted lethal levels. It is recorded that a man was given 60 cc of oil intravenously and survived after a stormy course. The state of the blood fats was not included.

CASE REPORT

W. D., age 38, had been well until two weeks before admission to the hospital when he suffered from an attack of "intestinal 'flu' " which responded to bed rest and conservative therapy in a few days and he returned to work. During the week prior to admission, some frequency of urination, some burning on micturition and urgency developed, but he continued at his work.

On the day of admission acute urinary retention developed and as his family doctor was unable to relieve this satisfactorily, due to the fact that attempts at catheterization were unsuccessful, he was sent into hospital. Further attempts to catheterize the patient were made shortly after admission, using all manner of catheters, filiforms and followers, sounds and finally the injection of approximately 7–10 cc of mineral oil through a catheter to the neighborhood of the bulbomembranous urethra. The catheter was passed to this site, and, using a two ounce bulb syringe, the small amount of oil mentioned was passed through the catheter under pressure exerted on the bulb syringe.

Due to failure to relieve the retention by these methods, the patient was well sedated and within a few hours a suprapubic cystotomy was done in the operating room under anesthesia.

Examination at the time of admission and immediately postoperative yielded few untoward signs. In retrospect the important findings noted were that the patient was somewhat flushed even on admission and had a faintly cyanotic appearance, and that his pulse rate, though regular, was rapid, the rate being around 120/min. Otherwise, the patient was in good condition, rational with normal chest findings and normal abdominal findings except for a distended bladder almost to the umbilicus preoperatively.

The day following his operation the patient felt well, though was restless with occasional sighing respirations. It was noted at this time that he had a low grade fever, basal rales in both lower lobes of lungs, some fine petechiae in the axillae bilaterally, and a bilateral Babinski sign. Pulse rate, 120–130/min.

Urinalysis showed only a faint trace of albumin, a positive benzedine test for blood; on microscopic examination, 10–15 white blood cells per high powered field, 10–15 red blood cells per high powered field centrifuged.

Blood work showed hemoglobin 87 per cent, white blood cells 11.7; smear normal; nonprotein nitrogen 35 mg. per cent; CO_2 combining power 37.2 volumes per cent.

The second day postoperatively the patient was clinically about the same though exhibiting intermittent dyspnea, and respiratory rate rose to 30/min.

A chest film showed a picture not unlike miliary tuberculosis, and indeed was reported as suggesting this condition, or carcinomatosis.

Spinal tap done showed clear fluid under normal pressure; subsequently to laboratory examination and to culture, no abnormal findings were apparent, and there was no bacterial growth.

Blood culture done this day was subsequently reported "*no growth*".

The third postoperative day the patient went rapidly downhill with rising respiratory rate, tachycardia up to 160/min., cyanosis and finally coma and death.

The autopsy shortly after death revealed the following major points:

1) The cause of the retention was a stone the size of a bean, measuring 1.3 by 0.5 cm., impacted in the bulbous urethra.

2) The cause of the acute respiratory difficulty and death was a patchy but massive intra-alveolar hemorrhage of the lungs. Many droplets of oil in the alveolar wall capillaries were responsible for this (fig. 1, *A*). The lungs, as a result of this process, were, in the gross, extremely distended and consolidated, and almost three times their normal weight. When fixed in formalin the cut surface had a greasy feel.

3) Similar capillary oil emboli were demonstrated in the kidneys, (fig. 1, *B*), myocardium and brain (fig. 1, *C*); and other effects produced by these emboli and proven by microscopic exam were petechiae of the spleen, skin, pleura, renal pelvis and urinary bladder.

Many of these sections were stained with scarlet red and sudan which have general lipoid affinities and with which the emboli stained a brilliant orange. Osmic acid, more or less specific for fatty acids, does not color the emboli and nile blue sulphate, a neutral fat stain, also does not stain the emboli. Depot fat stains black with osmic acid and pink with nile blue sulphate; paraffin oil does not stain with either one.

From the above clinical and pathological evidence and in view of the findings in literature concerning similar cases (Carr and Johnson; Patterson) it is believed with certainty that death in this patient resulted from the instillation of oil under pressure into the urethra. There was no gross disturbance in the urethra of this case suggestive of tear or false passage, as brought about by the manipulative efforts. To microscopic examination there was, of course, some edema and congestion evident at the site of the impacted stone, but no real break in the mucosa was demonstrated.

Despite the fact that the evidence here overwhelmingly points to the urethral instillation of oil as the cause of death, there are still many factors which can not be quite explained. It is not definite from gross and microscopic studies just how the mineral oil was able to pass into the circulation in an amount sufficient

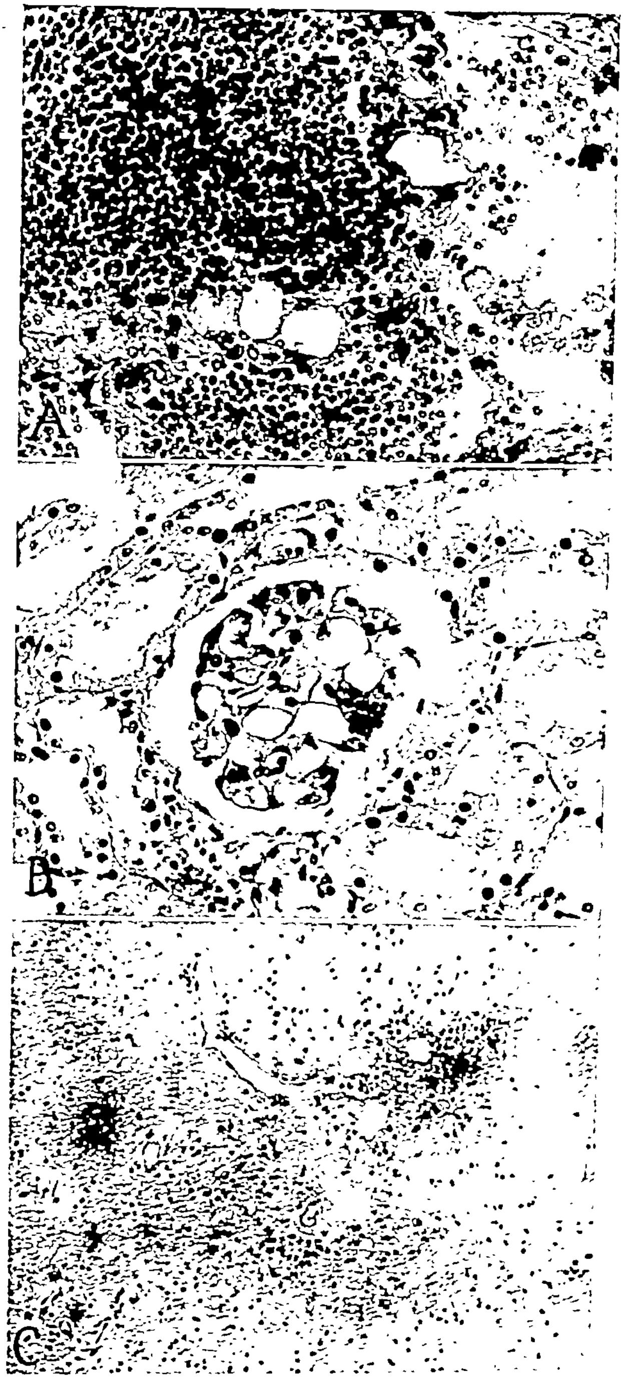

FIG. 1. *A*, lung showing two alveoli packed with red blood cells, and in intraalveolar wall are two fat (mineral oil) emboli (low center clear areas). *B*, kidney. Glomerulus and surrounding tubules. Mineral oil embolism evident in glomerulus as clear spaces where oil dissolved out during preparation. *C*, Brain tissue with small petechiae (black) and mineral oil emboli seen as clear round areas to right center (three).

to cause the widespread embolic phenomena. Could it be that even a few minims of oil so introduced provoke a biocheimcal upset in the tissue fats or the blood fats and cause them to form the lethal droplets in such profusion? If such an outcome as this can result with the use of a few cubic centimetrrs of oil as an aid to the difficult passage of a catheter, then why has this complication not been more common, for surely this procedure is not infrequently carried out?

It is known, of course, that the urethra is a very potent absorptive bed and reaction can occur from instillation of local anesthetic agents in this area. Many times bacteremia has resulted from manipulation of the urethra in the presence of infection, and it is known that air and water may be absorbed into the circulation during operative procedures in the posterior urethra. To this last may be added oil, especially as in this case, and the other reported cases, after a previous episode of manipulations has been attempted.

It is apparent that only a small quantity of oil is necessary to provoke serious disturbance and death. One cubic centimeter of oil will mathematically produce scores of millions of droplets, 10–15 microns in diameter, all of which are capable of blocking a capillary.

There is much to learn from this tragic case, and much yet to learn. There is also a definite warning to others who will find the treatment of urethral obstruction their problem.

CONCLUSION

A case of embolism as a result of urethral instillation of mineral oil to try and bypass urethral obstruction due to an impacted calculus in the urethra is presented. The outcome was fatal, and autopsy findings are sufficient to prove the etiology of the lesion and the cause of death.

Some remarks are made concerning fat embolism, its history and importance, and reference is made to three other reported cases in the literature, of similar cases of fatal outcome from urethral instillation of oil.

Thanks are extended to Dr. John Barrie and Dr. Ritchie of the University of Toronto Department of Pathology, under the direction of Dr. William Boyd, for their help and investigation in this case.

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AN INHALANT ANALGESIC OF ASSISTANCE IN MINOR UROLOGIC PROCEDURES

R. S. BREAKEY

The preparation to which I wish to call attention is trichloroethylene. This is not new, but I believe it is not known to most urologists. It was suggested to me by an otologist who had found it extremely helpful in office surgical procedures including myrinogotomy. There are few references to its use in American literature but a number in the British.

It alleviates anxiety to a marked degree and even in some cases produces a mild euphoria or sense of well being. While it has been used as a general anesthetic, in the dosage recommended for these purposes it does not produce unconsciousness. It is pleasant and nonirritating. The patient experiences a feeling of relaxation with often a tingling sensation or numbness of the extremities, and a variable sensation of vertigo. There is almost immediate recovery following its withdrawal. There occurs a definite loss of sensitivity; i.e., needle pricks.

While some patients are stoical, many are the reverse, and particularly in urologic practice, emotionally effervescent. Cystoscopy, urethral dilatation, spinal puncture, aspiration and injection of hydroceles, et cetera, are often greatly facilitated by its use and I would not now continue without it.

There are several commercial products. The one which we have used is Chlorylen produced by the Schering Corporation. One to one and a half cubic centimeters are sprayed upon an ordinary gauze sponge and the patient holds this just beneath the nose allowing some air space. After 10 or 15 respirations, instruments may be passed in cases where patients have previously refused either examination or treatment. I have used this upon myself and enthusiastically recommend it to all urologists.

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XANTHINE CALCULI: CASE REPORT

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Twenty-three cases of xanthine calculi have been reported. In all but three, the calculi have been removed from the bladder or have been recovered and analyzed after their spontaneous passage. In the three remaining cases the calculi have been removed from the pelvis of the right kidney. This marks the twenty-fourth reported case in which xanthine calculi have been found.

A 60-year-old white man, A. S. No. 507530A, was first seen at the Ohio State University Hospital on August 30, 1950. The patient stated that he had been aware of a persistent dull ache in the right flank for 3 weeks. He also thought hat he might have passed a small stone in the urine on several occasions during he preceding three year period. The remainder of the history was not contribuory or remarkable. Physical examination was negative except for mild right lank tenderness. Urine: specific gravity, 1.020; albumin, 1-plus; sugar 0; hite blood cells, 5–10 per high powered field; red blood cells, 20 per high owered field; stain, bacilli. An x-ray film of the abdomen revealed no calculi or ther abnormalities. Gantrisin was prescribed and the patient was advised to eturn in 2 weeks.

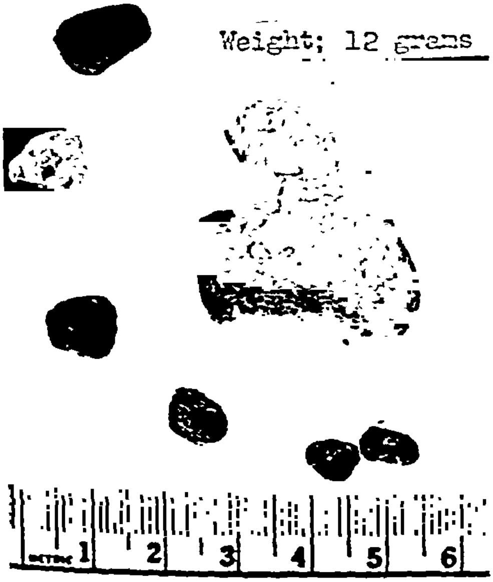

FIG. 1

The patient was next seen on October 18. He stated that the medicine had relieved him of the flank pain. Examination of the urine did show the absence of bacteria but it was abnormal in that it contained 25 white blood cells—20 red blood cells per high powered field. Excretory urography revealed a normal left side, and evidence of filling defects in the pelvis and calyces of the right kidney. Shortly thereafter, on retrograde pyelography, a faint outline of calculi in the region of the right kidney was noted and the pyelograms showed filling defects in the pelvis and calyces. A diagnosis of calculi in the right renal pelvis and calyces was made and pyelolithotomy was advised.

On December 27 the patient was admitted to the hospital for surgery. The interval history was not remarkable. Physical examination was negative. A chest film was normal. Laboratory studies were as follows: Urine: albumin, trace; white blood cells—5–10 and red blood cells 10–15 per high powered field; stain, bacilli and cocci. Blood studies: hemoglobin, 13.4 gm., red blood cells, 4.8 million; white blood cells, 9800; blood urea nitrogen, 14.5, alkaline phosphatase, 4.7 King-Armstrong units; phosphorus, 2.6 mg. per cent; calcium, 10 mg. per cent, uric acid, 4.0 mg. per cent. Separated renal function studies showed appearance *of phenolsulfonphthalein from the right kidney in 4 minutes and from the* left kidney in 3½ minutes with 10 per cent concentration from each kidney in 15 minutes.

Right pyelolithotomy and nephrolithotomy were carried out on December 29. A large y-shaped calculus was found in the renal pelvis and smaller ones in the calyces (fig. 1). They weighed a total of 12 gm. and were light brown in color.

Analysis of the calculi by the Department of Physiological Chemistry employing the Hawk method showed them to be composed of xanthine.

Since operation the patient has been asymptomatic and the urine has been normal. No follow-up pyelograms have been made.

SUMMARY

Another case in which xanthine calculi were found is reported. This case is unique in that the calculi recovered are by far the greatest in total weight as compared to the other reported cases of renal xanthine calculi.

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MODIFICATION OF THE ELLIK EVACUATOR

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The Ellik evacuator is one of the best and most popular bladder evacuators available to the urologist. By the addition of an emptying valve in the bottom and an air vent in the top, the Ellik evacuator can be made even more efficient, more rapid, and more easily operated than it has been in the past.

An evacuator so designed is capable of performing repeated bladder evacuations and of being emptied and refilled again and again without being detached from the resectoscope sheath. These functions are also accomplished without removing the bulb from the evacuator.

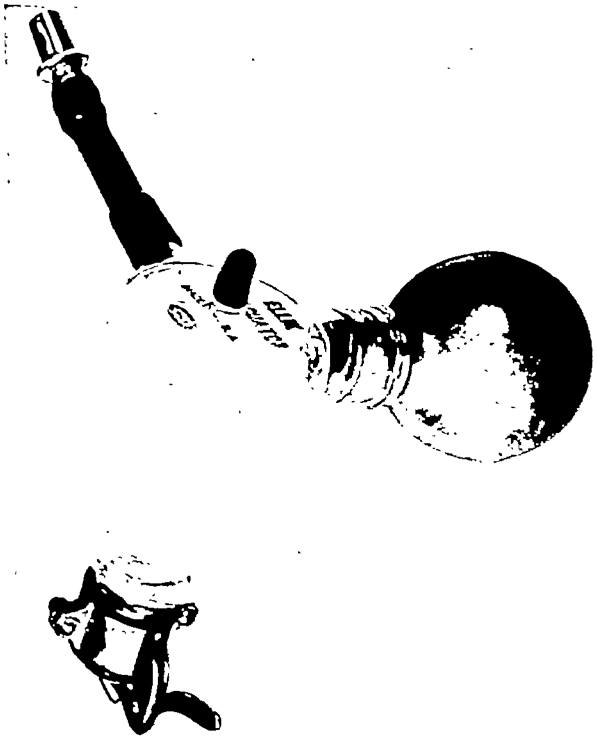

FIG. 1

In actual operation the evacuator is attached to the resectoscope sheath and the water is turned on. The air vent is opened and the glass bottle fills. As it fills, all of the air is forced out through the air vent so that no bubbles are introduced

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into the bladder. When the evacuator is completely filled, the air vent is closed and the bladder contents evacuated in the usual manner. To empty the evacuator the emptying valve is opened. Upon release this valve springs shut and the procedure is repeated. Throughout this entire process, the evacuator is held by the bulb in the right hand. The left hand is free to manipulate the water intake, the air vent, and the emptying valve.

Such an evacuator has been in constant use in our clinic for the past year and it has performed in a highly satisfactory manner.

I wish to express my appreciation to the American Cystoscope Makers, Inc. for converting these ideas into a workable instrument.

ANNUAL MEETING SOUTH CENTRAL SECTION, AMERICAN UROLOGICAL ASSOCIATION, HOT SPRINGS, ARKANSAS, SEPTEMBER, 29, 30 AND OCTOBER 1, 1952.

September 29

Splenectomy Associated with Surgery of the Left Kidney
N. B. Powell and James Bozzell, Houston, Texas
"Light" Pontocaine for Spinal Anesthesia in Renal Surgery
LeR. W. Lee and Edwin Davis, Jr., Omaha, Neb.
Tumors in Double Kidneys
H. E. Carlson, Kansas City, Mo.
Ureterovaginal Fistula
R. G. Carter, Austin, Texas
Injuries to the Ureter during Pelvic Surgery
J. H. Patterson, Denver, Colo.
Tumors of the Ureter
James Boyle, Memphis, Tenn. and I. S. Brown, Kansas City, Mo.

September 30

The T. Leon Howard Hour
Guest Speaker, Selected Subject—Richard Chute, Boston, Mass.
A Study of 200 Consecutive One-Stage Suprapubic Prostatectomies
R. K. Royce, St. Louis, Mo.
A Rational Approach to Prostatic Surgery
J. C. Cope, Columbia, Mo.
The Effect of Cortisone on Patients with Carcinoma of the Prostate
William Valk, Kansas City, Kans.

October 1

Perirenal Oxygen Insufflation by Retrorectal Route
James Headstream, Little Rock, Ark.
Urethral Diverticulum in Women
G. H. Teasley, Texarkana, Ark.
Blood Phenols in Renal Insufficiency
H. L. Warres, Laredo, Texas
Clinical Value of Urea Clearance and P.S.P. Tests
A. D. Mitchell, Kansas City, Mo.
Disorders of the Adrenal Cortex
G. F. Cahill, President of the American Urological Association.
The Case for Earlier Cystectomy in Carcinoma of the Urinary Bladder
J. J. Cordonnier, St. Louis, Mo.
Presidential Address: Harry M. Spence, Dallas, Texas.
Gross Hematuria in Sickle Cell Disease
H. G. Lung and Kenneth A. Forbes, St. Louis, Mo.
Leiomyosarcoma of the Kidney
Dale Atkins, Denver, Colo.
Rupture (Fracture) of the Penis
Robert F. Thompson, El Paso, Texas.
Renal Thrombosis
Horace Munger, Lincoln, Neb.
Bilateral Renal Artery Thrombosis
Joseph Fulcher, Tulsa, Okla.

ANNUAL MEETING, NORTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION CRUISE TO BERMUDA, SS OCEAN MONARCH, OCTOBER 5–10, 1952

OCTOBER 5

A CASE OF GOLDBLATT'S SYNDROME IN A BOY SIX YEARS OF AGE
A. Stillman, Montreal, Canada
DISCUSSION: H. C. ENGSTER, Troy, N. Y.
HYDRONEPHROSIS DUE TO DOUBLE RENAL VESSELS
G. F. Cahill, President, American Urological Association, New York, N. Y.
ROLE OF ANTI-HISTAMINES IN DIODRAST REACTIONS
G. E. Slotkin, E. G. Eschner and G. W. Fugitt, Buffalo, N. Y.
DISCUSSION: CLARENCE SCHNEIDERMAN, Montreal, Canada
RECONSTRUCTIVE SURGERY OF THE LOWER URETER
R. A. Hancock, Pittsburgh, Pa.
DISCUSSION: L. E. GIBSON, Syracuse, N. Y.
INFARCTS OF THE KIDNEY
J. S. Fitzgerald and P. S. Mullins, Utica, N. Y.
DISCUSSION: W. J. KENNEDY, Gloversville, N. Y.

OCTOBER 9

A STUDY OF NEUROBLASTOMAS
O. J. OBERKIRCHER, W. J. STAUBITZ AND F. J. PARMENTER, Buffalo, N. Y.
DISCUSSION: R. B. CARSON, Fort Lauderdale, Fla.
PRESIDENT'S ADDRESS: A PHYSICIAN'S DEBT TO MEDICINE
W. A. BARRETT, Pittsburgh, Pa.
ENURESIS
S. H. JOHNSON, III, Pittsburgh, Pa.
DISCUSSION: JOSEPH D'ERRICO, Niagara Falls, N. Y.
RADIATION TREATMENT OF CARCINOMA OF BLADDER USING FOLEY CATHETER TECHNIQUE
Grant Reid and C. A. Moore, Montreal, Canada
DISCUSSION: MAX RATNER, Montreal, Canada
RESULTS OF INCORRECT PATHOLOGICAL DIAGNOSIS OF CARCINOMA OF THE PROSTATE
A. E. Goldstein, Baltimore, Md.
TREATMENT OF LATE RELAPSE IN PROSTATIC CARCINOMA BY CORTISONE
W. G. Hayward, Jamestown, N. Y.
DISCUSSION: A. B. HAWTHORNE, Montreal, Canada
EXPERIENCE WITH RETROPUBIC PROSTATECTOMY
T. J. Lewis, John Knight and Spencer Servoss, Williamsport, Pa.
DISCUSSION: F. C. FARROW, Buffalo, N. Y.
METASTATIC CARCINOMA OF THE PENIS SECONDARY TO CARCINOMA OF THE RECTUM
H. L. Boyd, Rochester, N. Y.
DISCUSSION: W. B. GARLICK, Albany, N. Y.

ANNUAL MEETING, NORTH CENTRAL SECTION, AMERICAN UROLOGICAL ASSOCIATION, HOTEL RADISSON, MINNEAPOLIS, MINNESOTA, OCTOBER 8, 9, 10, 11, 1952

October 9

Prenatal and Neonatal Kidney
F. B. Bicknell, Detroit, Mich.
Papillary Tumors of the Renal Pelvis and Ureter
J. K. Sokol, Chicago, Ill.
Mesoblastic Nephroma in the Adult Complicated by Unilateral Hemoglobinuria
B. E. Fillis and Willard C. Meyer (by invitation), Evanston, Ill.
Special Basic Science Lecture: Applications of Basic Renal Physiology to Kidney Disease
K. G. Wakim (by invitation), Rochester, Minn.
Nephrocalcinosis, Clinical and Histopathologic Study (Collective Review)
J. D. Mortensen (by invitation), Rochester, Minn.
Urological Complications Following Abdomino-Perineal Resections of the Rectum
G. O. Baumrucker, Hinsdale, Ill.
Bladder Diverticula
H. W. Christensen, Wausau, Wisc.
Delayed Cystography
R. G. Bunge, Iowa City, Iowa
Carcinoma of the Seminal Vesicle
B. A. Smith, Jr., Minneapolis, Minn.
Malignant Transformation in a Tubular Adenoma
W. K. Hicks, Sioux City, Iowa
Irradiated Gold in Treatment of Carcinoma of Prostate
Rubin Flocks, Iowa City, Iowa
Adrenalectomy for Carcinoma of Prostate
W. J. Baker, Chicago, Ill.

October 10

Special Clinical Lecture: The Present Status of Surgical Procedures for Uretero-Enteric Anastomosis
A. W. Bohne, Detroit, Mich.
Total Cystectomy for Carcinoma of the Urinary Bladder
F. A. Lloyd, Chicago, Ill. and G. O. Baumrucker, Hinsdale, Ill.
Follow-up Studies of Ectopia Vesicae with Uretero-sigmoidostomy
R. A. Garrett and J. H. O. Mertz (by invitation), Indianapolis, Ind.
Significance of Pyuria in Children
C. W. Latchem, Des Moines, Iowa
Hunner's Ulcer in Children
H. P. McDonald (by invitation), Atlanta, Ga.
Brief Topics and Useful Aids (Three Minute Presentations)
A Simple Method of Providing Perineal Drainage in Operations on the Urinary Bladder
F. A. Lloyd, Chicago, Ill.
The Use of Trichlorethylene for Office Urology
B. H. Brunkow, Monroe, Wis.
Presentation of Waterproof, Plastic Disposable Cystoscopic Drape
G. L. Garske, Minneapolis, Minn.
A Simplified and Practical Penile Clamp
B. C. Corbus, Jr., Fargo, N. D.
Hydronephrosis of Pregnancy Following Ureterosigmoidostomy
B. A. Smith, Jr., Minneapolis, Minn.
Ectopic Ureter Associated with Renal Duplication
E. Rupel, Indianapolis, Ind.
A Large Medullary Adrenal Tumor
H. G. McGavran, Quincy, Ill.
A New Ureteral Meatome for Use with the Resectoscope
R. G. Bunge, Iowa City, Iowa
Post-Cystectomy Wound Drainage
J. C. Sargent, Milwaukee, Wis.

THE EFFECT OF CORTISONE ON HUMAN SPERMATOGENESIS
N. J. Heckel, Chicago, Ill.
KNEE ACTION CORD HOLDER
E. F. Cummings, Oshkosh, Wis.
RETROCAVAL (CIRCUMCAVAL) URETER
V. C. Laughlin, Cleveland, Ohio
PROSTATIC CALCULI AND PROSTATIC CARCINOMA
N. O. Brink, Bismarck, N. D.
SUBARACHNOID URETERAL ANASTOMOSIS
L. Christofferson (by invitation) and B. C. Corbus, Jr., Fargo, N. D.
APPARATUS FOR CARE OF INVOLUNTARY URINATION AND INCONTINENCE WITHOUT A CATHETER
H. E. Miller, Minneapolis, Minn.
ONE-STAGE SUPRAPUBIC PROSTATECTOMY WITH PRIMARY CLOSURE OF THE BLADDER
G. H. Ewell and J. L. Mueller (by invitation), Madison, Wis.
LIPOMATOUS RETROPERITONEAL TUMORS, UROGRAPHIC FINDINGS
J. H. DeWeerd (by invitation), Rochester, Minn.
GUEST SPEAKER: THE INTERRELATION OF RENAL CYSTS AND TUMORS
T. E. Gibson, San Francisco, Calif.
PRESIDENTIAL ADDRESS: LITHOLAPAXY
Reed Nesbit, Ann Arbor, Mich.

OCTOBER 11

SYMPOSIUM ON THE ARTIFICIAL KIDNEY
The Management of Renal Insufficiency: An Evaluation of Conservative Methods and the Role of the Artificial Kidney

1. Introduction
   C. D. Creevy, Minneapolis, Minn.
2. The Conservative Treatment of Renal Failure
   Roy Swann, New York, N. Y.
3. Description of the Artificial Kidney of Kolff with Recent Improvements
   E. J. Lewis, Minneapolis, Minn.
4. Application of External Dialysis with the Artificial Kidney to the Treatment of Renal Insufficiency
   J. P. Merrill, Boston, Mass.
5. Experiences with the Leonard-Skeggs Artificial Kidney in a Community Hospital
   W. A. Keitzer, Akron, Ohio
6. Summary: The Place of the Artificial Kidney in Research and Treatment Today
   J. H. Harrison, Boston, Mass.

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RENAL INFARCTION

WILLARD C. MEYER, MAJOR (M.C.) U.S.A.R. AND
ARNOLD L. AHNFELDT, COLONEL (M.C.) U.S.A.

From the U. S. Army Hospital, Camp Carson, Colorado

Renal infarction as a clinical entity is one which is rare, but yet of significant incidence to warrant a consideration of the problem by the urologist. This condition may be of arterial, venous or traumatic origin. The three types of infarction will be further developed and a case secondary to trauma presented. A review of the literature indicates the case herewith presented of traumatic origin is the seventh such case on record.

Infarction of the kidney secondary to arterial occlusion has been found to be the most common type. In such cases, the cause is a result of emboli stemming from a cardiac lesion. In a series of 14,411 autopsies, renal infarction was diagnosed clinically in only two of the cases. Of the 205 cases in which renal infarction was found, a cardiac lesion was present in 76 per cent of the cases. In a series of 242 cases with bacterial endocarditis, 55 or 23 per cent were found to have embolic infarction of the kidneys. Bilateral infarction was found in 102 cases. In the remaining cases of unilateral involvement distribution was seen to be comparable. In another series of 143 autopsy records in which renal infarction was reported, the age group of between 30 and 50 predominated. Sex distribution was equal, and cardiac disease was reported in 95 per cent of the cases. The diagnosis of an arterial renal infarction can be made with the complaint of sudden onset of pain of renal distribution, a nonfunctioning kidney on the involved side, normal renal architecture by retrograde pyelogram, the presence of albuminuria and hematuria and most significant finding, the presence of heart disease. Such infarctions are usually sterile and result in a partial or complete loss of the involved kidney. The prognosis depends upon the amount of kidney tissue destroyed and the state of the remaining functioning tissue. Arterial infarctions are also seen following cholecystectomy, appendectomy, hysterectomy, and hernia repair; however, such incidence is low when compared with those associated with cardiac disease. Litten, in 1880, and Westerborn, in 1937, demonstrated that temporary ligation of the renal artery for more than one and one-half hours is followed by a complete renal necrosis. Ligation of the renal artery for a shorter period results only in edema and hyperemia of the kidney. Thus it can be seen that such an occlusion of the renal artery by an embolus would result in renal destruction, either partial or complete, before collateral circulation or organization and canalization could take place. Traube is credited with making the first clinical diagnosis of renal infarction in 1856. The case was one of rheumatic heart disease with aortic insufficiency. Death ensued nine days after the onset of symptoms which included pain in the right thigh. Post-mortem examination revealed many small infarctions of both kidneys.

Venous obstructions with secondary renal infarction are less frequent than those of arterial orgin, but are far more serious. The arterial infarction is usually aseptic and self limiting. The venous infarction is usually septic and associated with septic states. It is often bilateral or, if initially unilateral, progresses to a bilateral end. The kidney in this condition is usually enlarged and palpable as a result of the active congestion. Gross hematuria is also a frequent finding. The condition must be considered in the presence of septic states and progressive occlusion of the major venous channels. Retrograde pyelograms in this condition frequently show filling defects of the renal pelvis. In view of the frequent massive involvement of renal tissue with subsequent destruction in this condition, the condition is usually pre-terminal or is followed by azotemia and uremia, with death a late sequella.

The third and most rare type of renal infarction is that secondary to trauma. A review of the literature has indicated only six such reported cases. In such cases the diagnosis is frequently made as a result of the urinary tract survey indicated by the history of trauma and the presence of hematuria. In the study of renal trauma, a course of management is indicated which will conserve renal tissue for the patient. Indications for an early operation following renal trauma are those of massive hematuria which caused shock prior to replacement therapy, abdominal and thoracic injuries which require investigation, clinical or x-ray evidence of extravasation, and wide separation of renal segments or lacerations of the renal pedicle. Indications for late surgery following renal trauma are those of persistent urinary tract infection resulting from defects produced by the earlier trauma, hydronephrosis which resulted from trauma, and urinary tract calculi. Case reports reviewing the earlier renal infarctions secondary to trauma described a nonfunctioning kidney associated with hematuria following the injury. At surgery, 50 per cent or more of the renal tissue was found to be destroyed and the kidney removed. A presumptive diagnosis of partial or total unilateral infarction can be made with a history of trauma associated with hematuria. The pyelograms may be within normal limits. Such a case could be treated with watchful waiting and, in the event a correct diagnosis was made, an autonephrectomy would take place. However, in many cases the patient has subjective complaints referable to the affected side. Hematuria persists, and a definite diagnosis cannot be made. In such instances renal exploration is justified and surgery carried out on the basis of the condition found at time of operation, keeping in mind conservation of renal tissue.

CASE REPORT

A 28 year old white woman was admitted July 4, 1951 to the U. S. Army Hospital, Camp Carson, Colorado, following an automobile accident. Physical examination revealed many severe contusions to the left flank. A chest x-ray and a plain urogram were within normal limits. Her abdomen was soft and nontender. The patient had gross total hematuria associated with some bilateral lumbar pain. In that the patient was able to void spontaneously, had no suprapubic pain and could empty her bladder, it was believed that the hematuria was of renal origin. She was treated conservatively with bed rest; her blood pressure, pulse and hematocrit were followed closely and were normal at all times. Twenty-four hours after the injury the urine was clear and free of red blood cells by microscopic examination. Five days after the injury the bed rest was discontinued and retrograde pyelograms (fig. 1) made at cystoscopy. It was found the bladder was within normal limits, good function was seen from the left kidney by indigo carmine study, but no dye could be seen from the right ureteral orifice after 30 minutes. A catheter was placed in the right renal pelvis for a 24 hour period; no evidence of function from this kidney could be demonstrated. Renal architecture was within normal limits bilaterally, as seen in the retrograde pyelograms. Excretory urography revealed a normal left kidney and no function from the right kidney. The problem presented was one of unilateral nonfunctioning kidney which was of renal or prerenal origin. The past history did not reveal previous

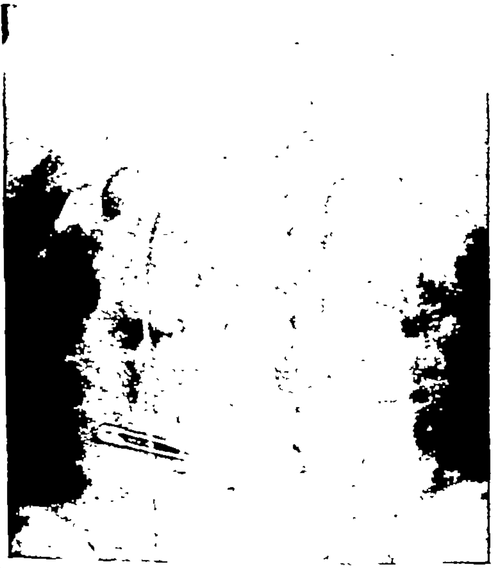

FIG. 1. Retrograde pyelogram, 5 days after injury. No significant abnormality of right renal architecture.

urinary tract disease. A recent bout of hematuria had occurred secondary to an accident in which the primary site of injury was contralateral to the involved kidney. Repeated physical examination was again within normal limits except for contusions of the left flank and a mild degree of hirsutism noted on the arms, legs and face. A male distribution of pubic hair was seen. However, the patient stated this condition had been present as long as she could remember and that her menstrual periods had been regular with a 4 day flow and a 28 day interval. She stated that her sexual life had been active and without change. Her blood pressure was within normal limits and no evidence of cardiac murmurs could be found. An electrocardiogram was reported as negative. Laboratory studies were essentially negative. In view of the nonfunctioning right kidney and the hirsutism a perirenal air insufflation was done under local anesthesia to further outline the right kidney and associated adrenal gland: no abnormalities could be detected. X-rays of the skull were also within normal limits. The patient was observed for approximately a 30 day period during which time no evidence of urine could be seen coming from the right kidney. The patient had some generalized lumbar pain but was otherwise symptom free. She continued to have unilateral anuria which was prerenal in origin.

It was believed that renal exploration was indicated, and this was accomplished on August 2, 1951. The right kidney was found to be within normal limits as to size, but was surrounded by extensive fibrotic adhesive bands suggesting a recent inflammatory process. The kidney parenchyma was soft in its consistency and appeared a mottled gray-brown color. The renal pedicle was palpated and no pulsation could be found in the renal artery. The renal artery was seen to be markedly reduced in size, being one-third the calibre of the normal vessel. The renal vein appeared to be within normal limits. It was decided that the pathological process existed in the renal artery, which had been occluded, and that total renal destruction had taken place. It was further believed that the patient would be best served by a nephrectomy, which was then done.

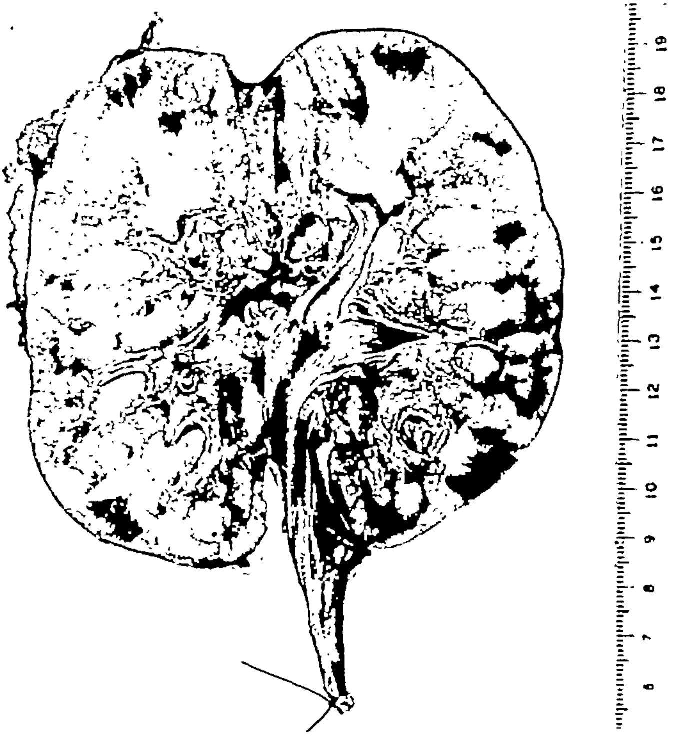

FIG. 2. Right kidney. Note mottled surface with local congestion and hemorrhage.

The postoperative course was uneventful until the seventeenth postoperative day, 12 days after ambulation was initiated, when the patient began to complain of pain in the left calf and thigh. The complaints were associated with a temperature elevation, a rapid pulse and a positive Homan's sign. A diagnosis of thrombophlebitis of the left superficial calf vein with possible extension to the major veins of the thigh and left pelvis was made. In view of this diagnosis, she was placed on anticoagulant therapy, with heat, rest and elevation to the affected part. Daily doses of dicumerol were continued for approximately 21 days. The patient was then ambulated and is now symptom free and has returned home, having received maximum benefit of hospitalization at this time.

Tissue examination of the specimen by the pathologist resulted in a diagnosis of "ischemic infarction due to thrombosis of the renal artery." Gross findings were that of a right kidney (fig. 2), the cortex measured 0.2 to 0.4 cm., the medulla measured 1.5 cm. The kidney weighed 90 gm. Several of the larger arteries were thrombosed and showed local hemorrhage in their walls. Microscopic examination revealed the normal architecture of the kidney to be completely obliterated. The tubules and glomeruli appeared as ghost structures staining brighter pink with eosin. No viable functioning renal parenchyma could be found in any section; the large branches of the renal artery showed various stages of thrombosis and fibrous obliteration. There were thrombi in the lumens which were invaded by fibroblasts and which had undergone canalization. The arteries throughout the kidney showed medial and intimal thickening of arteriosclerosis. Fat stains were negative except for the small amount of fat normally present during necrosis. Stains for amyloid were negative. The kidney specimen by both gross and microscopic examination was compatible with infarction due to an occlusion of the renal artery.

SUMMARY

The problem of renal infarction of arterial, venous and traumatic origin has been presented. The incidence of arterial infarction is the highest of the three forms discussed and is associated with cardiac disease. The prognosis in such cases is good and is dependent upon the extent of the kidney tissue involved. Venous infarction is usually found in septic states and in ascending occlusions of the major venous channels. The condition is frequently bilateral and the prognosis is grave. The third cause for renal infarction is trauma. This condition is quite rare; six previous cases have been reported in the literature, and the case report included increases this total to seven. In cases of traumatic infarction the diagnosis can be made by history of trauma with associated hematuria and unilateral nonfunctioning kidney. In those cases not coming to postmortem, a renal exploration was done with subsequent nephrectomy. In the case presented, the trauma was inflicted primarily upon the contralateral side. Subsequent nephrectomy revealed a total infarction of the kidney secondary to occlusion of the renal artery of recent origin, presumptively secondary to the trauma. In such cases of unilateral anuria of prerenal origin the possibility of peri-arteritis nodosa involving the renal artery and thrombo-angiitis obliterans have been reported and must be considered; however, with a history of extensive trauma with associated hematuria, ischemic renal infarction secondary to occlusion of the renal artery is the most likely diagnosis. Renal exploration is indicated in these cases where symptoms persist in order to substantiate the diagnosis and perform whatever surgery is indicated to conserve all functioning renal tissue.

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APLASTIC KIDNEY WITH ECTOPIC URETERAL ORIFICE IN THE PROSTATIC URETHRA

L. F. HUFFMAN

The following case report of an ectopic ureteral orifice seemed worthy of being placed on record because of its association with renal aplasia and because of the unusual procedure required for establishing the diagnosis.

CASE REPORT

A man aged 33 years was seen June 6, 1949 with the complaint of slight urethral discharge which he had had at intervals for several years. Six years previously he had nonspecific urethritis and left epididymitis. Two years ago he had another attack of urethritis which persisted in spite of penicillin therapy. The left epididymitis recurred 6 months previously. He had had a slight dull pain in the left side of the abdomen for fifteen years. Personal history was otherwise negative.

On examination there was slight moisture at the meatus. Urine was cloudy in both glasses. Specific gravity 1.012, pH 5.5, sugar negative, albumin trace, 3 white blood cells and 1–2 red blood cells per high power field. There was moderate induration of the epididymis on each side. The prostate was slightly enlarged, normal in contour and the prostatic fluid at that time showed a large amount of white blood cells. At a subsequent examination the fluid appeared to be normal.

On June 14, 1949 excretory urograms were made using 25 cc neo-iopax solution (fig. 1). A plain x-ray showed that the right kidney shadow was normal in position, rather large. No renal shadow was seen on the left. Excretory urograms showed the right kidney pelvis and ureter normal, no visualization of the left urinary tract. On cystoscopy in the office June 18, 1949 the right ureteral orifice appeared slightly hyperemic. No left ureteral orifice was recognizable. There was a rounded pale prominence on the left side of the trigone. Probing and search for a ureteral orifice on the left side of the trigone and left side of the prostatic urethra were unsuccessful. Patient was admitted to Fairview Park Hospital on June 24, 1949.

On June 27, 1949, under spinal anesthesia, a No. 24 Brown-Buerger cystoscope was passed. The bladder was normal except for slight generalized cystitis and absence of a left ureteral orifice. In the region of the left side of the trigone there was a moderate protrusion of the posterior bladder wall. The mucosa was normal except for slight inflammation presumed to be due to previous probing in search of an orifice. The instrument was withdrawn into the prostatic urethra and the protrusion of bladder wall on the left side was seen to involve the vesical orifice as well as trigone. Search for an accessory ureteral orifice in the prostatic urethra was unsuccessful. A No. 28 Stern-McCarthy resectoscope was passed and four or five bites of tissue taken in the region of the normal location of an ureteral orifice finally cutting through to a mucosa-lined cavity. After some difficulty with catheters impinging on the margin of this cavity, a No. 8 catheter could be passed a distance of 10 cm. obtaining a continuous flow of about 10 cc of

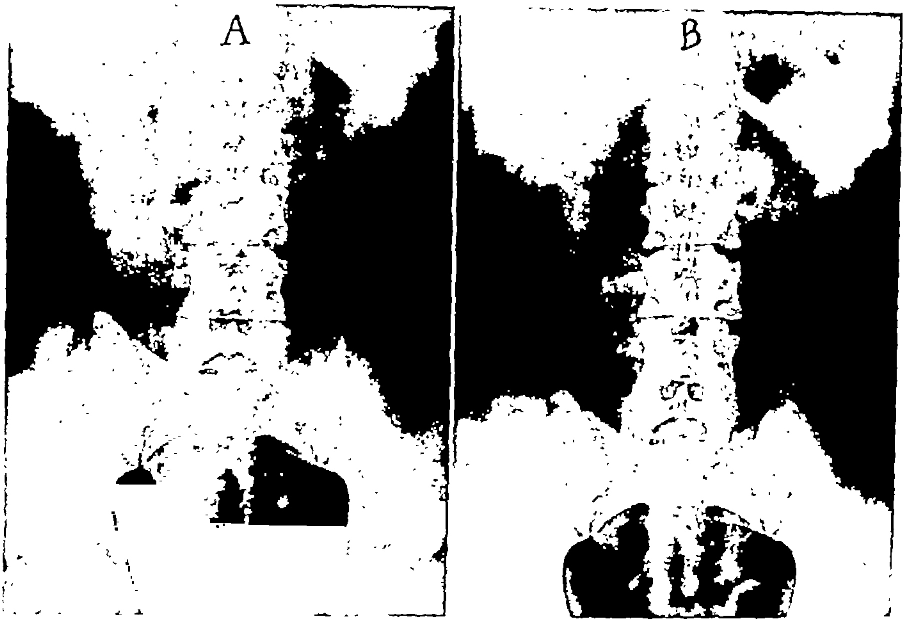

Fig. 1. *A*, plain x-ray of kidneys, ureters and bladder. *B*, excretory urogram. Normal right urinary tract. No visualization on left.

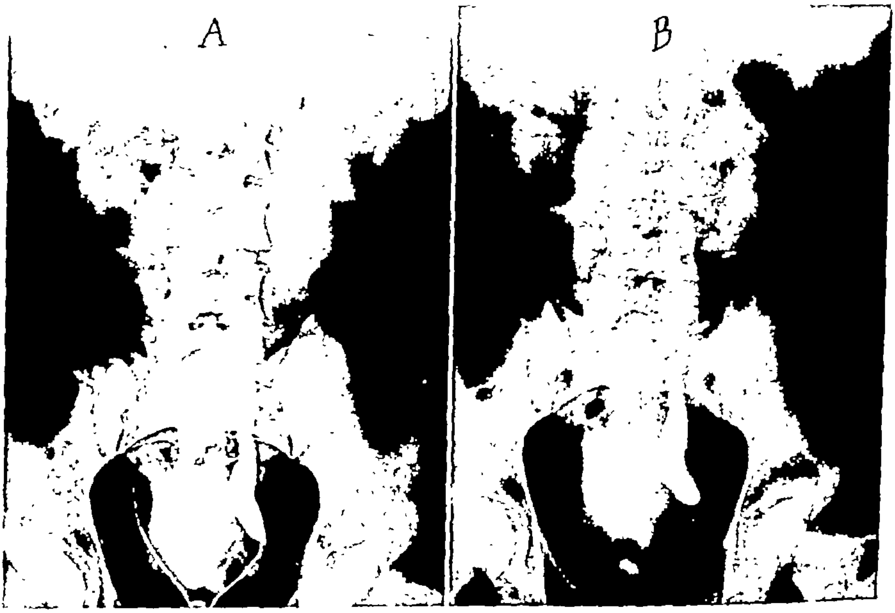

Fig. 2. *A*, retrograde urogram. Left ureteral catheter coiled in dilated pelvic portion of ureter. *B*, retrograde urogram. Catheters withdrawn.

purulent fluid. Upon its withdrawal a No. 5 catheter could be passed 30 cm. A retrograde left pyelogram was made through this catheter using 25 cc of 15 per cent skiodan solution (fig. 2).

The x-ray report is as follows: "Plain film with a ureteral catheter in the left side of the bladder shows the right kidney to be fairly well outlined and to be in a normal position. There is no distinct left kidney shadow. There is no evidence of urinary calculus. Retrograde pyelograms with the right catheter in the distal ureter and later withdrawn, and with the left catheter coiled in the left distal ureter show a good visualization of the right urinary tract which has a normal appearance. There is a marked uniform dilatation of the distal 10 cm. of the left ureter which is filled up to the level of the lumbosacral junction. Above this level, no definite dye shadow is seen. From the point where the left ureterovesical junction is supposed to be, a band-like dye shadow extends toward the central suprapubic region which may be the region of the prostatic urethra. This band-like shadow is quite smooth in contour and has the appearance of a dilated ureter. These findings indicate a congenital anomaly of the left ureter which appears to extend into the urethra. The opening through which the catheter was inserted had been made artificially on cystoscopy. The position and condition of the left kidney cannot be determined on the basis of this examination. E. Beyer, M. D., roentgenologist."

On June 27, 1949, left nephro-ureterectomy was performed. The customary oblique left lumbar incision for exposure of the kidney was made. No recognizable kidney was found. The dilated left ureter was isolated from surrounding structures as low as possible and followed cephalad to its attachment to an amorphous mass of tissue presumed to be the remnant of the left kidney. The vascular attachments were divided and ligated and the aplastic kidney with attached ureter brought out the lower extremity of the lumbar wound. The muscles were approximated with interrupted sutures of No. 1 chromic catgut in two layers and skin closed with silk. The patient was then placed in the supine position and an oblique extraperitoneal incision made in the left lower quadrant. The ureter was isolated, followed low down behind the bladder, clamped, severed, ligated and withdrawn from the lumbar incision. The wound was drained with a piece of Penrose tubing. Muscles and fascia approximated with interrupted sutures of chromic catgut. Skin closed with clips.

The pathological report was as follows: "The fresh specimen consists of a kidney measuring 4.5 by 2.5 by 1 cm. Attached to this is the ureter measuring 24 cm. in length and up to 0.8 cm. in thickness. The kidney with some attached fibro-adipose tissue weighs 10 gm. The surface which can be considered as that of kidney shows mottled red and brown tissue. The capsule is so densely adherent to the surface that separation is almost impossible without tearing renal tissue. It is soft to slightly firm and sections with ease to show brownish-gray tissue. Recognizable renal structure is not in evidence. Coming out one aspect of this is the ureter. The wall of the ureter measures up to 2 mm. in thickness and the circumference ranges up to 1.6 cm. The lining of the ureter is mottled red and gray. Representative portions are embedded.

"Microscopic description: Sections of the specimen considered to be kidney do not show any of the recognizable architecture. The sections merely show a large fibrous mass scattered throughout which are tubules of varying sizes and in small numbers. These are lined by columnar epithelium and contain eosinophilic stained hyaline tissue. There is considerable lymphocytic and mononuclear infiltration throughout. Occasional tubules resembling those of a kidney can be seen in some places but definite glomeruli appear to be absent. Sections of the ureter show some thickening of the wall and a marked infiltration of lymphocytes and monocytes of the mucosa. There is no evidence of a malignancy.

"Diagnosis: Aplasia of kidney showing chronic inflammation of remnant. John S. Mackrell, M.D., pathologist."

Convalescence from operation at first uneventful was complicated by secondary hemorrhage which required reopening the wound, evacuating clots and drainage on the sixteenth postoperative day. Thereafter, the incision healed promptly. The patient was discharged from the hospital on July 27, 1949 and has remained well.

SUMMARY

A case of aplastic left kidney with its ureter opening in the prostatic urethra treated by nephro-ureterectomy is reported. When the ureteral orifice could not be found, an opening was made with the Stern-McCarthy resectoscope from the bladder to the pyo-ureter into which a ureteral catheter was passed and retrograde ureterogram made.

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THE LEWIS STONE FORCEPS: AN AID TO URETEROLITHOTOMY

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The exasperation of chasing a small stone up and down a ureter during ureterolithotomy, and the lack of an efficient method of fixing both the stone and the ureter have prompted the design of this instrument.

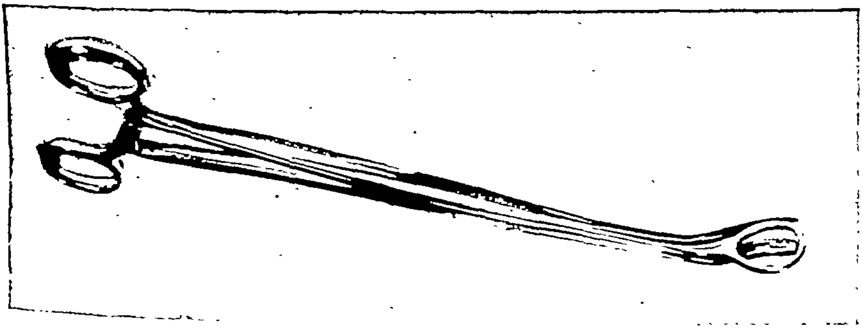

FIG. 1

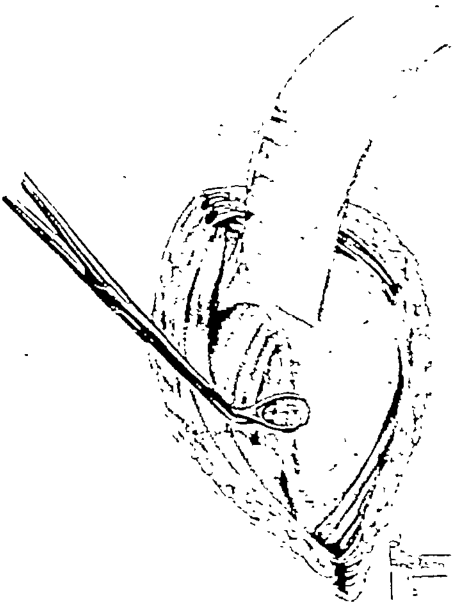

FIG. 2. Application of instrument in lower ureter. Counterpressure blade is shown in ghost. Line of incision is shown by interrupted line.

Many models were made before the final model was selected for production. The requirements for the forceps were: 1) It should not pinch tissue enough to damage the peritoneum, bowel or ureter. This would obviate the necessity of isolating the ureter. 2) It should hold the stone and ureter in fixed position; 3) It should have no sharp points or edges, 4) It should be curved to allow the application with one hand with the finger of the opposite hand fixing the stone.

This instrument fulfills all these requirements. The model was given to the C. R. Bard Company and they have made an excellent replica which answers all the author's desires.

The only criticism is that the loop is too small. However, any stone in the ureter which is too large for the present size is not going to be freely movable. The present size has been found to be most applicable.

TECHNIQUE

A small muscle splitting incision is made over the site of the stone as shown on an x-ray made just prior to surgery. The peritoneum is reflected from the body wall until the ureter is seen. The stone is palpated in the ureter with the index finger of the left hand; the loop is then placed over the stone and the blade closed from beneath to the first rachet only. A small incision is made over the stone.

The lower blade will expel the stone and it can be picked up with a long thumb forceps. The ureter may or may not be closed as desired. A drain is placed to the site and the wound closed.

By not freeing the ureter the objection to making an incision over the stone is countered due to maintenance of good blood supply.

The Lewis stone forceps is presented and recommended to the urological profession.

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RETROCAVAL URETER: CASE REPORT AND A NEW DIAGNOSTIC APPROACH

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Retrocaval ureter is an interesting anomaly which is rapidly ceasing to be a urological oddity. The case presented here appears to be the fourty-fifth such case reported.

In 1940, Pick and Anson[1] surveyed the literature and found a total of 27 cases including their own. Of these 27 cases previous to 1940, 19 were observed at postmortem and 8 at operation. Of the 8 operated cases, 4 had nephrectomies, 1 a nephrolithotomy and in 3 cases a corrective procedure was done with apparent recovery.

In 1940, Harrill[2] reported the twenty-eighth case from the Brady Institute. This was the first case to be diagnosed preoperatively and successfully repaired by section and re-anastomosis of the ureter, with a splinting catheter and pyelostomy drainage. Harbach[3] found a case at operation in 1940. A nephrectomy was done because of severe renal damage and infection. John DeCarlo, Greenwald and Surks[4-5] discovered the 30th and 31st cases in cadavers. Wilson[6] in 1941 reported a case found at operation in which a nephrectomy was done rather than a repair. Greene and Kearns[7] in 1946 made the second correct preoperative diagnosis and did a successful repair by transecting the ureter just below the pelvis and re-anastomosing it around a splinting catheter. Nephrostomy drainage was instituted rather than pyelostomy drainage, as advocated by Harrill. Lowsley[8] in 1946 divided the ureter just behind the bladder, freed it from beneath the vena cava and re-implanted it into the bladder. Subsequently, the lower ureter sloughed and a cutaneous ureterostomy was done. The third preoperative diagnosis was made by Goyanna and Counseller[9] in 1946 in a 33 year old male. A repair was successfully accomplished with transection and re-anastomosis of the ureter over a splinting catheter with nephrostomy drainage. In 1946, Nourse[10] reported a case found at operation in a Naval Hospital. A repair was done with transection of the ureter and re-anastomosis over a splinting catheter with pyelostomy drainage. Five months later a nephrectomy was done because of infection and hydronephrosis. In 1947, Young [11] reported a case found at operation in a 24 year old dwarf. A calculus was removed from the post-caval portion but

[1] Pick, J. W. and Anson, B. J.: J. Urol., 43: 672–685, 1940.
[2] Harrill, H. C.: J. Urol., 44: 450–457, 1940.
[3] Harbach, F. O.: N. Y. State Med. J., 40: 800–802, 1940.
[4] DeCarlo, J.: J. Urol., 45: 827–831, 1941.
[5] Gruenwald, P. and Surks, S. N.: J. Urol., 49: 195–201, 1943.
[6] Wilson, C. L. and Herzlich, J. J.: J. Urol., 51: 14–18, 1944.
[7] Greene, L. F. and Kearns, W. M.: J. Urol., 55: 52–59, 1946.
[8] Lowsley, O. S.: Surg., Gynec. & Obst., 82: 549–556, 1946.
[9] Goyanna, R., Cook, E. N. and Counseller, V. S.: Proc. Staff Meet., Mayo Clinic, 21: 356–360, 1946.
[10] Nourse, M. H. and Moody, H. C.: J. Urol., 56: 525–529, 1946.
[11] Young, J. N.: Brit. J. Urol., 19: 22–28, 1947.

since no obstruction was present the ureter was left alone. No hydronephrosis was noted in 8 months later.

McElhinney and Dorsey[12] correctly diagnosed and repaired a retrocaval ureter in a Naval Hospital on Guam in 1945. Pyelostomy drainage rather than nephrectomy drainage was instituted with apparent success. Creevy[13] in 1948 reported the fifth case to be diagnosed preoperatively. He used two separate incisions, one abdominal and one lumbar and accomplished a successful repair as evidenced by a beautiful 3 year follow-up pyelogram. Shearer[14] in 1949 reported the sixth preoperative diagnosis and successful repair utilizing essentially the same operation as described by Harrill. Heslin and Mamonas[15] reported 4 additional cases; three were confirmed surgically and one by x-ray diagnosis.

It would thus appear that the case reported here represents the eighth preoperative and the tenth successful repair.

EMBRYOLOGY

The embryological defect producing this anomaly has been thoroughly studied by numerous able investigators. As clinical urologists, we are concerned primarily with what we can do to help a kidney so skillfully neglected by mother nature. During fetal life the permanent kidney, having developed in the pelvis, ascends to the upper lumbar level, passing through a ring of venous channels. According to McClure and Butler[16] the vertebral limb of the ring is formed by the lumbar division of the pos-cardinal vein while the dorsal limb is a derivative of the supra-cardinal vein and the subcardino-supracardinal anastomosis. Normally the postrenal portion of the vena cava arises from the dorsal limb of the perimetanephric ring, the ureter thereby being placed in the antecaval position. In the anomalous arrangement one of the following developmental alterations occurs: 1) The ventral, rather than the dorsal limb persists, the ureter then being postcaval. 2) The dorsal limb fails to arise at all with similar results.

CASE REPORT

H. P., a white man, aged 23, was admitted to the Urological Service of the Hospital, University of Pennsylvania on August 12, 1948, with a complaint of right flank pain. Except for one episode of hematuria 15 years before admission, he had been asymptomatic until January 30, 1940. Pain lasting 3 days had then developed in the right lower quadrant. On July 3, 1948 he noted cloudy urine and was told by his family physician that he had pyuria and should have a urological investigation.

The right kidney could be felt on palpation but was nontender. Otherwise the physical examination was negative. Urinalysis showed 40–50 white blood cells per high powered field. An excretory urogram showed normal function of the left kidney. The right kidney was involved in a large hydronephrosis and hydro-ureter in the upper segment with a horseshoe shaped deformity overlying McBurney's point. The lower segment of the ureter was not visualized.

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[12] McElhinney, P. P. B. and Dorsey, J. W.: J. Urol., 59: 497–500, 1948.
[13] Creevy, C. D.: J. Urol., 60: 26–30, 1948.
[14] Shearer, T. P.: J. Urol., 62: 152–157, 1949.
[15] Heslin, J. E. and Mamonas, C.: J. Urol., 65: 212–222, 1951.
[16] McClure, C. F. W. and Butler, E. G.: Am. J. Anat., 35: 331–389, 1925.

At cystoscopy the bladder appeared normal. Indigo carmine appeared promptly from the left ureteral orifice in 4 minutes but in poor concentration from the right ureteral orifice in 15 minutes.

A 6F ureteral catheter met a complete obstruction 15 cm. above the right ureteral orifice. A retrograde pyelogram again revealed the previously described hydronephrosis and the catheter was observed to be lying directly over the vertebral bodies of L-4 and L-5. The entire right ureter could not be visualized.

The retrograde pyelogram was again repeated at which time the right ureteral orifice was occluded with a Ravich tip catheter and the upper urinary tract was filled with skiodan. Films revealed that the ureter ascended over the vertebral bodies of L-5 and 4, and L-3. Otherwise the hydronephrosis and upper ureter appeared much the same as in previous films. At this point a diagnosis of retrocaval right ureter was made (fig. 1, *A*).

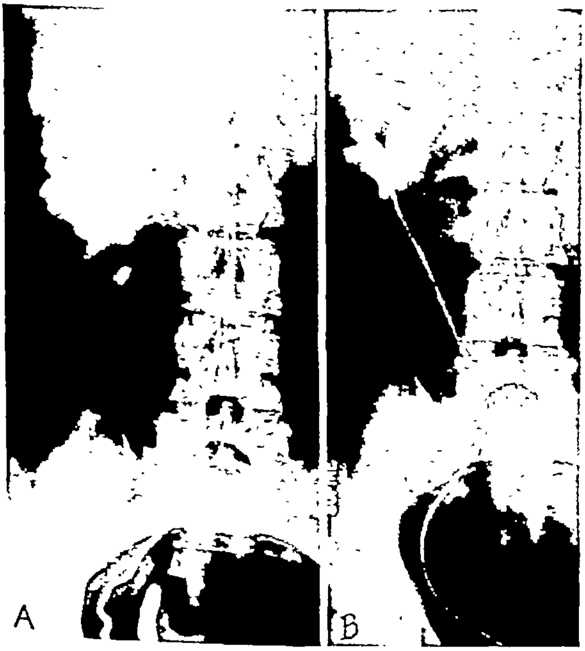

Fig. 1. *A*, preoperative retrograde pyelogram with Ravich tip catheter. This demonstrates S-shaped curve of ureter, as described by Randall and Campbell. Middle ureter overlies vertebral bodies of L-3, 4 and 5, with definite obstruction just lateral to body of L-3. *B*, retrograde pyelogram 6 months after operation. Correction of S shaped curve of ureter is shown.

A right flank incision was made extending from a point 4 cm. anterior to the transverse process of the first lumbar vertebra extending forward and medially parallel to the lower border of the twelfth rib and over the abdominal wall to a point 4 cm. anterior and medial to the anterior superior spine of the ilium. The muscle layers were divided in the usual manner. The peritoneum was retracted medially and the lower pole of the kidney was exposed. A large, dilated ureteropelvic junction was visualized and completely cleared of all adhesions. The upper ureter was freed downward to the point where it disappeared beneath the vena cava. The lower ureter was then located and dissected upward to the point where it also passed beneath the vena cava. It was found that the ureter could be completely freed beneath the vena cava so as to move freely in either direction. The ureter was obliquely divided about 4 cm. below the ureteropelvic junction and the lower segment removed from behind the vena cava. A one layer anastomosis of the ureter was accomplished with 00000 chromic swaged catgut. Through a pyelotomy incision a 10F soft ureteral catheter was inserted down the ureter nearly to the bldader. A 22F mushroom catheter was left indwelling in the renal pelvis for nephrostomy drainage. A ring of gelfoam gauze was placed about the anastomosed line. At the end of the operation there was considerable redundancy of the upper ureter and pelvis. This was not resected. The nephrostomy tube and ureteral catheter were brought to the outside through the posterior margin of the wound. The incision was closed in the usual manner around one Penrose drain.

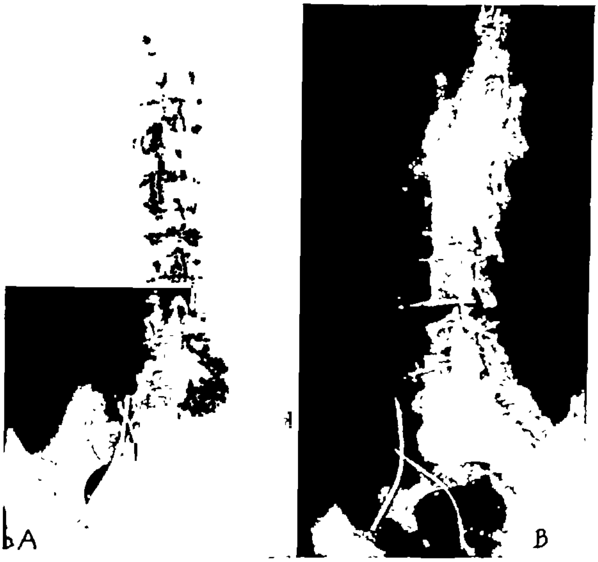

FIG. 2. *A*, in cadaver, catheter has been placed in vena cava through basilic vein. Ureteral catheter has been placed in right ureter to renal pelvis. This film demonstrates normal relationship between ureter and vena cava, with ureteral catheter crossing caval catheter just lateral to L-5. *B*, oblique film of experimental retrocaval ureter constructed in cadaver reveals that there are three points at which ureteral catheter is seen to cross caval catheter. This would seem to be almost 100 per cent diagnostic of retrocaval ureter.

The postoperative hospital course was smooth. At no time was his temperature over 100F. Fifteen days after the operation the ureteral splinting catheter was removed. On the twenty-first day the nephrostomy tube was injected with 5 cc methylene blue and clamped. The dye appeared in the voided urine promptly. The nephrostomy tube was removed. There was no drainage through the wound after the removal of the nephrostomy tube. Throughout the 21 day period of drainage the urine remained clear and upon removal of the nephrostomy tube no calcium deposits were seen. This was attributed to large doses of sodium acid phosphate which markedly decreased the urinary excretion of calcium. The patient was discharged from the hospital twenty-three days after operation.

One month later the ureter was easily dilated to 12F and a slightly hydronephrotic drip of clear urine was obtained. At the end of six months the renal pelvis had nearly returned to normal size and after one year intravenous urography revealed only minimal stasis (fig. 1, *B*). The patient was asymptomatic and the urine remained clear and free of infection.

The diagnosis of retrocaval ureter has heretofore depended primarily upon two pyelographic findings: 1) medial displacement of the right ureter over the vertebral column; 2) an S-shaped curve of the ureter, as described by Randall and Campbell.[17]

Since it is now a relatively simple procedure to affect renal vein catheterization for purposes of determining renal clearances of various substances the notion was conceived that perhaps such a procedure might be useful in aiding the diagnosis of retrocaval ureter.

In order to determine what added information could be gained from such a procedure, a series of cadaver experiments were performed in which a 10F renal vein catheter was threaded down the vena cava and into the right iliac vein. At the same time a 6F ureteral catheter was placed in the ureter to the renal pelvis, demonstrating the normal relationship between the ureter and the vena cava with the ureteral catheter crossing the caval catheter just lateral to L-5 (fig. 2). Another series of experiments were then carried out in the cadaver in which a retrocaval ureter was constructed. The ureteral catheter which was passed appeared to lie medial to the caval catheter until it crossed just lateral to L-3. The S-shaped curve of the ureter was again demonstrated. In the oblique film of the experimental retrocaval ureter it was revealed that there are three points at which the ureteral catheter appeared to cross the caval ureter (fig. 2, *B*). This would seem to be diagnostic of retrocaval ureter. In the lateral film it was noted that there were two apparent crossing points where the ureteral catheter crossed the caval catheter. Except for a higher crossing point in the lateral film, there seemed to be little difference in the diagnostic value of lateral films.

CONCLUSIONS

Retrocaval ureter should be suspected in all cases of hydronephrosis associated with a medial deviation of the ureter.

The gentle S-shaped curve continues to be a very helpful diagnostic sign.

A one stage loin incision with oblique section and re-anastomosis of the ureter around a splinting catheter, accompanied by nephrostomy and pyelostomy drainage and chemotherapy, seems to be most favorable for success.

Catheterization of both vena cava and ureter may be of value when the diagnosis of retrocaval ureter is questionable.

A case of retrocaval ureter diagnosed preoperatively and successfully treated is presented.

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[17] Randall, A. and Campbell, E. W.: J. Urol., **34**: 565, 1935.

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CONGENITAL URETERAL VALVE: ITS ROLE AS A PRIMARY OBSTRUCTIVE LESION: CLASSIFICATION OF THE LITERATURE AND REPORT OF AN AUTHENTIC CASE

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Although almost all classifications of anomalies of the ureter include congenital ureteral valve, it is usually considered that it rarely, if ever, occurs as a primary obstructive lesion. Wolffer[1] first directed attention to their existence in 1887 with a report in which autopsy examination of 100 newborns revealed the presence of 20 ureters with 'more or less definite cross folds'. Subsequent studies by Englisch,[2] Robinson,[3] and Gerard[4] report lower occurrence and most authors accept 5 per cent as the likely incidence of ureteral valves in the newborn. These structures are vestigial remnants that disappear early in life and are considered by most investigators[5, 6] as unlikely to be responsible for obstruction of the ureter. Reduplication of the ureteral mucosa with formation of kinks and valves is not infrequently seen in tortuous dilated ureters in which a primary obstructive factor exists lower in the urinary tract with secondary kinking and valve-like formation. Rolnick[7] believed the case of Gottleib[8] to be the only authentic case in which the valve was responsible for obstruction, although he states: "Unfortunately, no drawing of the specimen accompanies the report, so it is uncertain whether the valve was primary or secondary to a kinking of the ureter by a hydronephrosis."

Since no previous survey of the literature has been reported, the following criteria are proposed in evaluation of cases to determine their authenticity as *primary* lesions responsible for obstruction of the ureter: 1) anatomically demonstrable transverse folds of ureteral mucosa which contain bands of smooth muscle; 2) changes of obstructive uropathy above valve, with normal urinary tract below; 3) no other evidence of mechanical or functional obstruction.

These criteria were used in analysis of reported cases. A total of 11 cases were reviewed, 4 of which were found to meet the above requirements (table 1). The case of Barclay and Baird[9] was considered by the authors to be obstructive, but since no anatomical studies were made and obstruction existed at two different levels, it is impossible to differentiate from ureteral stricture, and is therefore not used. Vermooten[10] (case 4) describes the surgical excision of bilateral congenital valves in a 16 month male, but unfortunately, no description of the lower urinary tract, other than mention of the fact that the bladder wall was moderately

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[1] Wolffer, J.: Arch. klin. Chir., **21:** 694, 1887.
[2] Englisch, T.: Deut. Zeitschr. f. Chir., vol. 2, 1789.
[3] Robinson, B : Medical & Surgical Monitor, 1903.
[4] Gerard: Thèse de Paris, No. 63, 1908.
[5] Caulk, J. R.: J. Urol., **9:** 1, 1923.
[6] Eisendrath, D. N. and Rolnick, H. C.: Textbook of Urology. Philadelphia: J. B. Lippincott Co., p. 537, 1943.
[7] Rolnick, H. C.: Practice of Urology. Philadelphia: J. B. Lippincott Co., p. 558, 1949.
[8] Gottleib. J.: Ztsch. urol. Chir., **26:** 301, 1929.
[9] Barclay, I. B. and Baird, M. C.: Lancet, **2:** 1171, 1935.
[10] Vermooten, V.: J. Urol. **41:** 455, 1939.

TABLE I

NO.	YEAR	AUTHOR	AGE	SEX	SIDE	TYPE	LOCATION	SECONDARY CHANGES	ASSOCIATED ANOMALIES	METHOD OF DIAGNOSIS	TREATMENT
1	1927	Hunner, G. L.	12	F	L	'Cusp shaped'	Junction lower third and middle third	Moderate hydro-ureter	Reduplication of ureter containing valve	Surgery — ureterectomy with section of valve	Ureterectomy (good result)
2	1927	Cabot, R. C.	13	M	R	'Exactly like valves of veins'	6 cm. from bladder	Massive hydronephrosis and dilated ureter	None	Autopsy	Nephrostomy (patient died)
3	1929	Gottlieb, J.	23	F	R	'Like aortic valve'	Just below uretero-pelvic junction	Massive hydronephrosis with normal ureter below valve	None	Autopsy	Nephrostomy (patient died)
4	1945	MacLean, J. T.	20	M	R	Annular with pin-point opening	Junction of upper and middle third of ureter	Moderate hydronephrosis and hydro-ureter above lesion	None	Surgery—(valve described by operator)	Incision of ureter at site of valve leaflets—ureter closed and splinted—(good result)
5	1951	Wall and Wachter	½ yr.	M	L&R	Annular with pin-point opening	Lower third ureter	Bilateral hydronephrosis and hydro-ureter	None	Surgery with excision of valve and autopsy	Bilateral T-tube ureterotomy (patient died)

thickened, is given, and therefore the possibility of lower tract obstruction is not excluded. Ostry[11] reported a case in which a valve was found in the upper third of the ureter, but is not included as dilatation of the urinary tract existed below rather than above the lesion.

ETIOLOGY

The etiology of congenital valves is unknown. The embryological studies of Rudolph Chwalla[12] indicate the presence of an occluding membrane at the distal end of the ureter in utero, the persistence of which is offered as the probable genesis of ureteroceles and hydronephrosis in the newborn. These studies demonstrate that in the 12 mm. human embryo, an epithelial spur or furrow appears on the cranial side of the primary excretory duct and extends downward closing off the lumen of the ureteric bud. This epithelial membrane persists until approximately the 30 mm. stage at which time metanephric urinary secretion begins and the membrane is ruptured by pressure ischemia, re-establishing ureteral patency. The existence of a physiologic obstruction of the distal ureter with spontaneous release at 19–25 days was confirmed in mice by Brown.[13] It is postulated that incomplete persistence of such a fold may explain congenital valves in the distal ureter. This theory would be applicable in the case here reported; however, it is noted the occurrence of this lesion is not limited to the distal ureter, and could not be considered as the etiology in primary valves in the upper ureteral segments.

PATHOLOGY

The term valve implies the presence of a structure which permits passage in one direction but not in the opposite. As an anatomical structure, it is used to denote a transverse fold of the membrane and when applied to the ureter is defined as a transverse fold of mucosa containing bands of muscularis.[14, 15] It must be differentiated from congenital ureteral stricture in which the lumen is narrowed without structural changes of the mucosa.

Valves may occur at any level of the ureter. Table 1 [8, 16, 17, 18] indicates that their occurrence as primary obstructive lesions is approximately equal in the three ureteral segments in this small series.

The gross appearance is usually that of an annular ring with a pin-point opening. An exception is the case of Hunner,[16] in which the valve was 'cusp' shaped rather than the usual appearance of an iris diaphragm. Microscopically, the leaflets contain all layers of the ureter except the adventitia.

CASE REPORT

M. P. M., a white male infant, was born February 9, 1950 in another hospital 7 weeks before estimated date of maturity and weighed 1900 gm.

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[11] Ostry, H.: Treatment Serv. Bulletin, 2: 56, 1947.

[12] Chwalla, R.: Urol. & Cutan. Rev., 31: 499, 1927.

[13] Brown, A.: Am. J. Anat., 47: 117, 1931.

[14] Campbell, M. F.: Textbook of Pediatric Urology. New York: The Macmillan Co., 1937.

[15] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926.

[16] Hunner, G. L.: J. Urol., 15: 57, 1926.

[17] McLean, J. T.: J. Urol. 54: 374, 1945.

[18] Cabot, R. C.: Boston Med. & Surg. J., 196: 276, 1927.

The physical examination at birth revealed no anomalies other than prematurity and slightly enlarged kidney masses. Progress was satisfactory for the first week of life with the baby voiding frequently but on the seventh day a sudden temperature rise to 40.2C accompanied by cyanosis was noted. Physical examination at this time revealed the kidneys to be somewhat larger than at birth and the bladder appeared to be distended. Catheterization produced purulent urine, a culture of which grew out B. coli. The nonprotein nitrogen was found to be 78 mg. per cent with a CO_2 of 28 volumes per cent. It was believed that the child had congenital urinary tract obstruction of some type and a suprapubic cystotomy was done on the ninth day of life. The baby's course was extremely labile for the following 3 months. The urine remained infected in spite of continuous administration of sulfonamides and antibiotics. High fevers were frequent and dehydration and anemia a constant threat, requiring many transfusions, parenteral fluids and almost continuous administration of oxygen. A cystogram made during the third month of life showed regurgitation at both ureteral orifices with dilated redundant ureters and hydronephrosis.

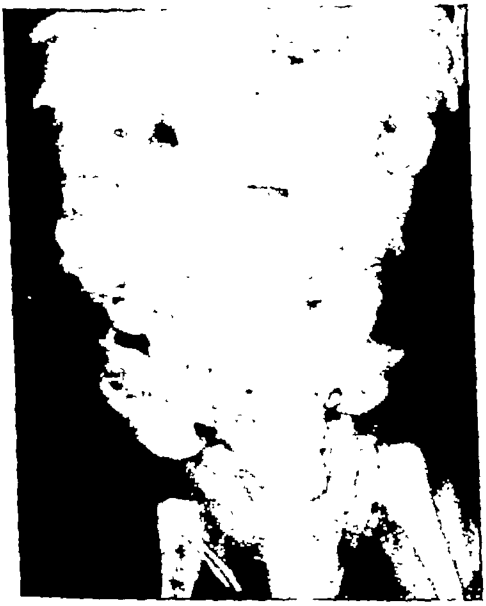

FIG. 1

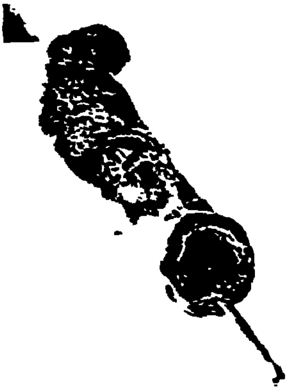

FIG. 2

FIG. 1. Voiding cystogram after right ureteroplasty with ureteral regurgitation showing bilateral hydronephrosis and tortuous dilated ureters, most marked on left.

FIG. 2. Gross specimen of excised 8 cm. segment of left ureter with annular valve leaflet visible in distal end, with probe protruding through the pinpoint ureteral lumen.

At four months the child was transferred to St. Louis Children's Hospital at which time he weighed 3440 gm. Physical findings were essentially the same with infected urine, nonprotein nitrogen of 143 mg. per cent, chlorides 130 meq. and the CO_2 was 22.7 meq. A cystogram made through the suprapubic tube at this time revealed no ureteral regurgitation. Since cystotomy had effected no improvement it was believed that supravesical obstruction existed and on June 24 the right side was explored, revealing a large dilated tortuous ureter and a massive hydronephrosis with a very thin renal parenchyma. A T-tube ureterostomy was done, excising approximately 10 cm. of redundant ureter from its middle third with primary end to end anastomosis. In placing the distal limb of the T-tube in the ureter, an obstruction was met approximately 3 cm. from the bladder which resisted passage to various sizes and types of catheters and probes. An incision made directly over the obstructing point revealed a valve-like membrane extending across the ureteral lumen which was excised with scissors allowing easy passage of the T-tube into the bladder.

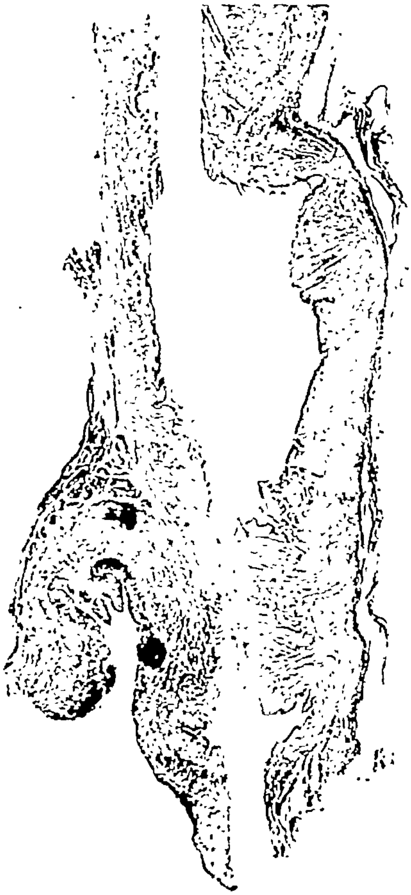

FIG. 3. Photomicrograph of longitudinal section of excised distal 4 cm. of left ureter showing valve leaflet containing smooth muscle protruding into ureteral lumen.

Postoperatively, the child had less fever, but very little improvement in his general condition was noted with persistence of the acidosis and no decrease in the nonprotein nitrogen. The T-tube was removed after 2 weeks and a cystogram then revealed bilateral reflux through both ureteral orifices with bilateral hydronephrosis and hydro-ureters, less marked on the right (fig. 1). A month after the operation the inadequacy of the right kidney to sustain life was apparent and it was felt that the only chance of survival would be to provide better drainage for the left kidney in the hope that parenchyma on this side might be less damaged. On August 10 the left side was explored, revealing findings identical to those on the right. A ureteroplasty also was done on this side, utilizing a T-tube, but the excised redundant segment was taken from the lower third of the ureter extending to approximately 2 cm. from the bladder and included a congenital valve identical to the one found on the right side (figs. 2, 3 and 4).

The immediate postoperative response was encouraging with the fall of the nonprotein nitrogen from 135 to 68.5 mg. per cent and temporary stabilization of the CO_2, but dehydration and anemia recurred and required repeated transfusions and constant vigil to maintain fluid balance. An occasional febrile episode occurred and on September 6, one month after the last operation, the child became suddenly cyanotic with severe acidotic breathing and in spite of supportive therapy, respiratory collapse followed and death occurred.

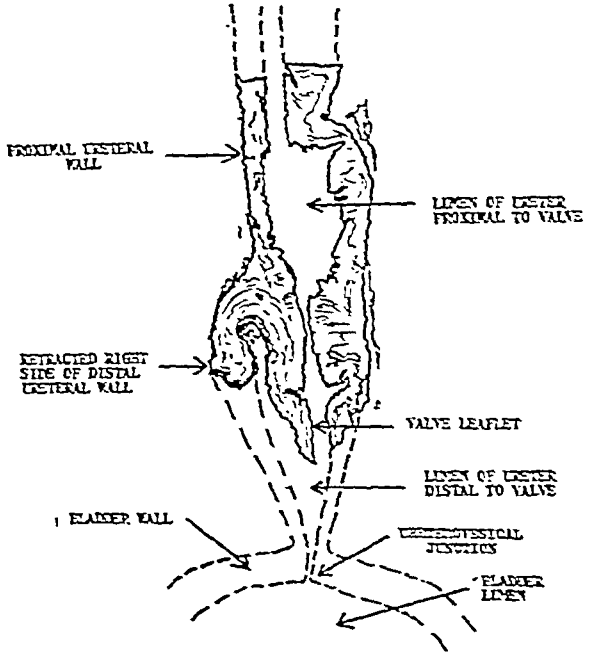
PROXIMAL URETERAL WALL
LUMEN OF URETER PROXIMAL TO VALVE
RETRACTED RIGHT SIDE OF DISTAL URETERAL WALL
VALVE LEAFLET
LUMEN OF URETER DISTAL TO VALVE
BLADDER WALL
URETEROVESICAL JUNCTION
BLADDER LUMEN

FIG. 4. Diagram of figure 3 showing relationships to bladder and proximal ureter.

The surgical specimen consisted of the distal 8 cm. of the left ureter containing an annular, iris type fold at the distal end with a pin-point opening, that would barely admit a fine silver probe (fig. 2). The ureter, due to its great size could be completely everted and the proximal surface of the valve was identical to the distal. The specimen was fixed and longitudinal sections made, demonstrating the valve leaflet within the lumen of the distal ureter (fig. 3) and diagram of same (fig. 4). The inverted appearance of the leaflet is due to retraction of the right side of the distal ureteral wall in the fixed specimen. The gross specimen (fig. 2) shows the actual 90 degree angulation of the valve leaflet.

Post-mortem examination revealed bilateral hydro-ureter and hydronephrosis with chronic and acute pyelonephritis with both ureters patent and healed anastomotic sites. Examination of the bladder revealed the bladder wall to be some what thicker than usual with reduplication of the mucosa due to prolonged cystotomy drainage. No trabeculation, cellules or other evidence of changes secondary to obstruction were present. The bladder neck admitted a finger tip and no abnormality of the urethra was present. Sounds could be passed with ease in both directions. In the right ureter, 3 cm. from the bladder, the approximate level at which the valve was excised, there was noted a longitudinal submucous tunnel 5 mm. long which was believed to be the original pin-point opening of the valve, the rest of the leaflet having been trimmed away at the time of surgery.

It is believed that the aforementioned findings justify the description of this lesion as the *primary cause of obstruction, i.e., pathological changes associated* with obstruction above the valves with a normal urinary tract below it. It is inconceivable that this lesion was secondary to one of the other causes that are frequently considered to be responsible for ureterovesical obstruction, such as a faulty neuromuscular mechanism or extrinsic factors such as peri-ureteral bands, etc.

SUMMARY

Congenital ureteral valves may be defined as transverse folds of redundant ureteral mucosa containing smooth muscle. They occur in approximately 5 per cent of newborn, usually do not obstruct the ureter and disappear early in life. *Rarely they may persist as primary obstructive* lesions, *occurring* in all ureteral segments. The etiology is unknown, the theory of Chwalla being presented as a plausable explanation. Their clinical significance is obvious, emphasizing the principle that *complete step by step urological study must be done in all children with obstructive uropathy in order to properly identify the level of obstruction.* This will permit prompt institution of the indicated measures to promote free urinary tract drainage, which is so essential in the preservation of functioning renal parenchyma in these patients.

CONCLUSIONS

Congenital ureteral valve does exist as a primary obstructive lesion.

A case of bilateral congenital ureteral valve is presented, the fifth authentic case of this type obstruction, and the first in which both ureters were involved.

Criteria are proposed for use in classification of congenital ureteral valves as primary obstructive lesions.

The incidence, etiology, pathology and clinical significance are briefly discussed.

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VESICO-URETERAL REFLUX IN PARAPLEGIC PATIENTS

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Spinal cord lesion is known as one of the causes of vesico-ureteral reflux.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] The importance of routine cystograms was advocated early.[12] Talbot and Bunts[7] demonstrated the detrimental effect of reflux on the upper urinary tract of paraplegic patients. The method of examination here presented consists of a combination of cystometry and concurrent cystography. This was performed in 238 random cases with lesions of the spinal cord, 56 (23.1 per cent) of which were found to have reflux.

REVIEW OF LITERATURE

A comprehensive review of the literature has been compiled.[7, 10, 13, 14, 15] Reflux is extremely rare, if it occurs at all, with a normal genito-urinary tract,[16, 17, 18, 19a,]

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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[15] Gruber, C. M.: a) A comparative study of the intra-vesical ureters (uretero-vesical valves) in man and in experimental animals. J. Urol., 21: 567–581, 1929. b) The ureterovesical valves. J. Urol., 22: 275–292, 1929. c) The function of the ureterovesical valve and the experimental production of hydro-ureters without obstruction. J. Urol., 23: 161–179, 1930.

[16] Randall, A. and Campbell, E. W.: In Modern Urology, edited by Cabot, Philadelphia: Lea and Febiger, 1936, vol. 2, pp. 258–261.

[17] Campbell, M. F.: Pediatric Urology. New York: The Macmillan Co., 1937, vol. 1; pp. 70–73.

[20, 21] it is not a constant phenomenon in paraplegics,[8, 10, 22a] but a high incidence is seen in cases with severe urinary tract disease such as hydronephrosis or urethral diverticulum.[7, 11] Anatomical changes of the bladder and ureteral orifices are recognized as the chief factors for the development of reflux;[7, 9, 23] however, neurogenic factors may be a cause also.[6, 10, 24]

METHOD OF EXAMINATION

Routine sphincterometry[25] and cystometry were performed with a Lewis cystometer. A 70 per cent sterile skiodan solution was used in order to fill the bladder, and x-rays were taken with each additional 50 cc introduced. The maximal volume was kept at 400 cc; by the time this volume was reached, a total of eight x-rays had been taken. The patient strained during exposure of every other film so that the pictures with even numbers corresponded to the "straining" phase of the bladder while those with odd numbers reflected the "relaxed" phase.

OBSERVATIONS

Among the 56 patients with reflux, 8 had injuries of the cervical cord, 33 of the thoracic cord, 9 of the lumbosacral cord and 6 patients had nontraumatic conditions of the spinal cord; (2 with multiple sclerosis, 1 with meningovascular syphilis, 1 with cord tumor and 2 with infectious myelitis).

The interval between the date of injury and detection of reflux ranged from 3–127 months and that between the onset of disease and first observation of reflux from 12–96 months.

Either reflex or volitional micturition was present in 33 of the traumatic and 3 nontraumatic cases. Five patients of the traumatic group had a cystostomy and 12 an intra-urethral catheter. Three patients of the nontraumatic group had intra-urethral catheters.

Twenty-five patients had a bilateral reflux, nineteen a right and twelve a left reflux. The ureteral orifices were normal in seventeen, pathological in 30 cases and were not mentioned in nine. Orifices were considered pathological when they were patulous, edematous, surrounded by cellules, trabeculations or diverticula.

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[24] Bors, E., Comarr, A. E. and Moulton, S. H.: The role of nerve blocks in management of traumatic cord bladders: Spinal anesthesia, subarachnoid alcohol injections, pudendal nerve anesthesia and vesical neck anesthesia. J. Urol., 63: 653–666, 1950.

[25] Bors, E.: A simple sphincterometer. J. Urol., 60: 287–298, 1948.

No correlation existed between the condition of the ureteral orifice and level of the cord lesion.

Reflux occurred in 52 individual instances with a volume of from 50–200 cc in the traumatic group and 9 in the nontraumatic group. Sixteen instances of reflux were found from 200–400 cc in the traumatic and 0 in the nontraumatic group.

The bladder capacity ranged from 50–100 cc in 9 cases, from 125–200 cc in 18, from 225–300 in 11 and from 325–400 cc in 18 cases.

The intravesical pressure with reflux ranged from 0–25 mm. Hg. in 54 examinations of the traumatic and in 3 of the nontraumatic cases. A pressure of from 40–112 mm. Hg. was noted in 14 examinations of the traumatic group and a pressure of 30–58 mm. Hg. was observed in 6 of the nontraumatic cases.

Capacity and intravesical pressure with reflux at a volume of 50 cc: The capacity ranged from 50–100 cc in 6 patients, from 125–200 cc in 11, from 225–300 cc in 5 and from 325–400 in 4; i.e. 17 patients had a capacity of 200 cc or less and 9 had a capacity of 200 or more. The detrusor tone ranged from 0–10 mm. Hg. in 13 cases, from 11–20 mm. Hg. in 3 and from 21–70 mm. Hg. in 9. The detrusor value of 1 case remained undetermined.

Reflux on straining occurred in 14 patients; it occurred at 100 cc in 3 cases which was identical with the bladder capacity. The lowest pressure was 8 mm. Hg. and the highest was 112 mm. Hg. High values of 104 and 112 mm. Hg. respectively occurred with contracted bladders of 100 cc capacity and severe abdominal spasticity. The low value of 8 mm. Hg. was seen in a patient with an incomplete lesion, the reflux was transient and disappeared with a volume of more than 200 cc.

In 35 patients, reflux produced a pyelogram; 14 had a bladder capacity of less than 200 cc and 21 more than 200 cc. Among the first group, nine had pyelograms at a volume identical with the bladder capacity and the same occurred in 5 of the second group. The vesical neck was open in eleven and closed in 10 patients of the second group. Pathological orifices were present in eleven of the first group, and in fourteen of the second group. The intravesical pressure of the first group ranged up to 10 mm. Hg. in 2 cases, from 30–90 mm. Hg. in 11 and 175 mm. Hg. in 1. In the second group the values were up to 10 mm. Hg. in 7, 11–30 mm. Hg. in 8 and 31–50 mm. Hg. in 5 cases.

The vesical neck was open in 28 patients and closed in 27; it was not recorded in 1. In 14 cases, the vesical neck and vesico-ureteral valve opened at identical values of volume and pressure; in 6 cases the vesical neck opened with higher values of volume and pressure and in 3 cases with lower values; in 4 cases the pressure remained the same, but the volume was either higher (2 cases) or lower (2 cases).

Appearance or disappearance and increase or decrease of reflux were observed in 6 cases without detectable causes. Reflux decreased when the low capacity of 100 cc was reached in 2 cases, both with cervical lesions. The capacity of 4 patients with dorsal lesions ranged from 200–400 cc. The intravesical pressure was high in 2 cases, with a cervical and a dorsal level respectively, and was normal in the remaining patients. Only 1 patient had pathological ureteral orifices.

The effect of surgical interventions revealed: reflux of 1 patient with a cervical lesion ceased after posterior rhizotomy from D-11 caudad.

A right ureterolysis was performed on a patient with a thoracic lesion and the patient benefited by this procedure clinically. Chills and fever disappeared; however, the x-ray evidence of reflux persisted.

Twenty-four patients with various cord levels underwent transurethral resections, but only 6 showed improvement: 4 lost the reflux, the fifth lost reflux unilaterally and the reflux of the other side disappeared following repair of a penoscrotal fistula. The reflux of the sixth patient subsided when good bladder function developed after resection and pudendal nerve anesthesia. Fourteen continued to have reflux after transurethral resection; the result remained undetermined in 4. Twenty-three patients suffered from pathological changes of the urethra at the penoscrotal junction. In 2 patients reflux disappeared postoperatively, though repair was attempted in 10.

DISCUSSION

Method. Talbot and Bunts[7] have introduced the "delayed" cystogram for the detection of vesico-urethral reflux. Our technique of "cystographic" cystometry is comparable to a method used by Barksdale and Baker[25] in animal experiments. It offers the advantage of a synchronized recording of morphological and physiological data.

Incidence. The incidence of 23.1 per cent (56 cases) reflux among a total of 238 patients was somewhat lower than the figures of Pate and Bunts[11] who found 33 per cent (39 cases) among 114 paraplegic patients. Talbot and Bunts[7] found reflux in 10 out of 15 patients in the presence of far progressed renal pathological changes.

Reflux and neurological level. Reflux was more common with cervical and thoracic lesions than with lumbosacral; however, when the neuronal involvement was considered among all patients, including the cases with subarachnoid alcohol block which causes a secondary lower motor neuron lesion, the ratio increased still in favor of the upper motor as against lower motor neuron lesion (42:14 or 3:1). This is difficult to explain, but some factors further our understanding: bladders resulting from lower motor neuron lesions are characterized by absent somatic innervation of the pelvic floor and functional loss of preganglionic parasympathetic fibers; the detrusor is weakened and rarely, if ever, capable of complete emptying contraction;[26] the sympathetic nerve supply is little, if at all, disturbed and the trigonal expansion of the ureteral muscles[27] retains its innervation. The normal tone tends to keep these structures competent during micturition by strain or crede. A different condition exists with an upper motor neuron lesion; then all three systems, somatic, parasympathetic and sympathetic act on a spinal level, and owing to frequently impaired coordination, imbalance of the respective muscle groups results. Neurogenic factors, then, contribute also to the development of reflux. A few authors support this theory[10] and quote Hoen's case in which reflux disappeared when the 11th intercostal nerve was connected with the third sacral. A relationship between reflux and nerve blocking procedures was described previously.[25] Other facts in support of the neurogenic theory are: reflux is not constant,[10, 25] it can be altered by tidal drainage or operative interventions which do not attack the ureteral orifices.[5, 11] In 6 of our cases reflux disappeared or appeared without operative intervention; in 4 cases, resection of the vesical neck cured the condition, and improved it in 2. Of 10 patients with penoscrotal lesions, only 2 benefited postoperatively by disappearance of reflux. Improvement of infection contributes to these results, and the pathological changes of the ureteral orifice and ureters must have been reversible.

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[26] Bors, E.: Urologic aspects of rehabilitation. J. A. M. A., 146: 225–229, 1951.

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Reflux and ureteral orifice. Several authors[7, 9] have pointed to anatomical changes at the ureteral orifice from infection as a frequent cause of reflux and we confirm their findings; however, reflux has been observed[6] with normal orifices also. An orifice may or may not be patulous.[8] Among our 56 patients, 17 or almost one-third had "normal" orifices. Bilateral disease of the orifices was not necessarily connected with bilateral reflux, a unilateral pathological orifice did not exclude bilateral reflux and normal orifices did not exclude unilateral or bilateral reflux. The morphological appearance of the orifice then is not an absolute criterion for the presence or absence of reflux. Therefore, either our cystoscopic means are inadequate or intrinsic neuromuscular factors are responsible which do not appear morphologically.

Reflux and bladder capacity. Reflux occurred almost as frequently with capacities of less than 200 cc as with more than 200 cc. Large bladder capacities occurred with lower motor neuron lesions. Although it would appear as if a small capacity is not more apt to develop reflux than a large capacity. Analysis of the cases with reflux at a volume of 50 cc demonstrated that among twenty-six, seventeen had capacities of less than 200 cc while only 9 had greater capacities. Reflux at a low volume, then is almost twice as frequent in small bladders than in large ones. Significantly 16 of the 17 patients with small capacity had upper motor neuron lesions, while 6 of the 9 with large capacities had lower motor neuron involvement.

Reflux and detrusor tone. Absolute values of detrusor tone at the first sign of reflux are inconclusive. Some information is derived from correlating detrusor value, reflux at a volume of 50 cc and bladder capacity. If 10 mm. Hg. at 50 cc volume is compatible with a normal detrusor tone, 13 or $\frac{1}{2}$ of the cases fitted this combination. Seven patients had an upper and six a lower motor neuron lesion. Of the 7 patients, four had a bladder capacity up to 200 cc and 3 above 200 cc. Only 1 patient had normal orifices. Of the 6 patients, three had a bladder capacity up to 200 cc and three above 200 cc. Three had normal orifices.

Twelve patients had elevated detrusor values of more than 10 mm. Hg. at a volume of 50 cc; seven with an upper and five with a lower motor neuron lesion. Only 2 of the five had an original lower motor neuron lesion, the remaining three underwent subarachnoid alcohol blocks without improvement of bladder capacity. The 7 patients with upper motor lesion had a capacity up to 200 and

2 of the 5 with lower motor neuron lesions had a capacity of above 200 cc. Only 2 patients had normal orifices.

Low detrusor values with reflux at minimal volume occur with almost equal frequency in a small or large bladder and the level of the lesion is irrelevant. In contrast, high detrusor values were predominantly associated with small bladders and upper motor neuron lesions. Pathological changes of the orifices were present in either group without prognostic value. Five cases with reflux at a volume identical with the bladder capacity had high detrusor values caused by the rigidity of the bladder wall. These findings confirm Prather's[28] or Herbst's[29] views that either sustained bladder tonus to resist distention or contracted hypertonic bladder cause reflux.

Reflux and strain. Reflux with strain occurred in 8 patients with upper and in 6 with lower motor neuron lesions. Five patients had a genuine lower motor neuron lesion with capacities from 300–400 cc and reflux occurred at volumes of 100, 200 and 300 cc respectively at a pressure of from 18 mm. Hg. to 64 mm. Hg. It is likely that the extrinsic pressure was responsible for the occurrence of reflux due to pathological orifices. The remaining case had undergone a subarachnoid alcohol block; the capacity was 150 with increased detrusor tone and this reflux cannot be ascribed to extrinsic pressure. The reflux of the 8 patients with upper motor neuron lesions was caused only indirectly by the extrinsic pressure of strain which is known to alter the detrusor activity of such bladders. Extrinsic pressure may be an indirect cause for the reflux in upper and a direct cause in lower motor neuron lesions.

Reflux pyelogram. Thirty-five patients had a reflux pyelogram, 23 with upper and 12 with lower motor neuron lesions. The pyelogram occurred at capacity in $\frac{1}{3}$ of the first and in $\frac{1}{6}$ of the second group. The capacity was below 200 cc. in $\frac{3}{5}$ of the first and in $\frac{1}{12}$ of the second group; pyelogram with strain occurred in an almost equal distribution, in $\frac{1}{2}$ of either group. The vesical neck was open in $\frac{2}{3}$ of the first and $\frac{2}{3}$ of the cases of the second group. The orifices were more often normal in the first than in the second group. The incidence of a pyelogram at capacity is more frequent with upper than lower motor neuron lesions. It does not depend on bladder capacity, since it occurs equally frequent with volumes below and above 200 cc, on the condition of the orifices, intravesical pressure, or radiographic condition of the vesical neck. Capacity, pressure and condition of the vesical neck reflect the type of lesion rather than causes of reflux pyelogram.

Reflux and vesical neck. The vesical neck was closed in 20 patients with upper and 7 patients with lower motor neuron lesions. The vesical neck and ureterovesical valve opened simultaneously in 10 patients with upper and 4 with lower motor neuron lesions, it opened later in 3 patients with upper and 3 with lower motor neuron lesions and it opened earlier in 1 case with upper and 2 cases with lower motor neuron lesions. It opened at the same pressure but lower volume, i.e. earlier, in 2 additional patients with lower motor neuron lesions while it opened at the same pressure but higher volume, i.e. later in 2 other cases with similar neurological findings. A simultaneous opening of neck and valve is more frequent with upper than lower motor neuron lesions, while the earlier or later opening of neck and valve respectively cannot be related to the neurological level.

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[28] Prather, G. C.: Vesico-ureteral reflux. Report of a case cured by operation. J. Urol., 52: 437–447, 1944.

[29] Herbst: Discussion.[2]

The fleeting appearance or disappearance of reflux could not be connected with either the neurological or urological condition and needs further study.

Reflux and urethral disease. We confirm that urethral disease and reflux appear frequently together in two-fifths of our cases. Repair of the urethral lesion "cured" reflux in 2 of 10 operatively treated patients with relatively recent injuries, suggesting that the control of infection was more important than intervention.

Reflux and posterior rhizotomy. The disappearance of reflux after posterior rhizotomy is the more interesting as the ureteral orifices were pathological and remained so postoperatively. We presume that the effect of interruption of all afferent pathways from D-11 caudad acts on the reflex arcs of the ureter, the trigone and detrusor. No similar report could be found and this experience lends further support to the neurogenic theory of the etiology of reflux.

Disappearance of reflux after ureterolysis[5] did not occur in our case although the patient improved clinically.

Reflux and transurethral resection. We observed disappearance of reflux following transurethral resection.[7] Four patients (3 with lower and 1 with an upper motor lesion) and 2 additional patients benefited from this procedure when it was combined with auxiliary interventions (correction of penoscrotal lesion and pudendal nerve anesthesia respectively). The orifices of all 6 cases were normal, and in these patients bladder neck obstruction with incoordination of forces of expulsion and retention was at least in part responsible for reflux. The low percentage of success confirms Bumpus's[2] observation that reflux is rare from mere obstruction of the vesical neck.

SUMMARY

A method is presented which combines simultaneous cystometry and cystography and which was applied at random in 238 patients. Fifty-six (23.1 per cent) of these had vesico-ureteral reflux, among them 50 with injuries to spinal cord or cauda equina and 6 with spinal cord disease.

Reflux was bilateral in 25 patients, on the right side in 19, and on the left side in 12; it appeared or disappeared without detectable reason in 6 patients.

The ureteral orifices were pathological in 30 patients, normal in 17 and not mentioned in 9 patients.

Reflux occurred more frequently in patients with upper motor lesions than with lower motor lesions (42:14 or 3:1).

Reflux at a low volume of 50 cc was observed almost twice as frequently with small than with large bladders, and the findings of Prather and Herbst are confirmed that either sustained detrusor tone or contracted bladders are contributory to reflux.

Extrinsic pressure (strain) is believed to be an indirect cause of reflux with upper and a direct cause with lower motor neuron lesions.

A pyelogram through reflux developed in one-third of the patients with upper and in $\frac{1}{6}$ of those with lower motor neuron lesions.

No causative relationship could be detected between opening of the vesical neck and appearance of reflux.

Penoscrotal fistula or diverticulum accompanied two-fifths of the cases with reflux; however, reflux disappeared in only 2 of the 10 patients whose urethral lesion was corrected.

Reflux in 1 case disappeared after a complete posterior rhizotomy from D-11 caudad despite the presence of pathological orifices.

Reflux was altered (disappeared or became unilateral) in only one-fourth of the 24 patients who underwent transurethral resection of the vesical neck.

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BLADDER DIVERTICULUM IN THE FEMALE

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In recent months, 4 cases of bladder diverticula in the female have been observed in the urological service at Kings County Hospital. This led us to review the occurrence of these cases at this hospital and compare the incidence with reports from other clinics. From January 1, 1940 to July 31, 1946, there were 12,036 urological cases. Of these, a total of 88 vesical diverticula were observed, of which six were in the female. This incidence of 1 female to 13 males results in a percentage of 6.8 per cent of all diverticula of the bladder as occurring in the female. Eisendarath and Rolnick[1] report a ratio of 1 female to 10 males. Herman[2] found 8 cases of bladder diverticula in the female in a total of 10,441 urological cases. Schacht and Crenshaw[3] report that 3.2 per cent of all diverticula of the bladder, in their series, occur in the female while Kutzmann[4, 5] reviewing the literature since the beginning of the century, reports 3.4 per cent.

CASE REPORTS

Case 1. No. 21481, 1944, Kings County Hospital, W. E., a 23 year old woman, was admitted with the complaints of frequency, urgency and dysuria. Two years prior to admission she had hematuria which did not recur. When an infant, an operation was performed for spina bifida. Cystoscopy, on admission, revealed bladder neck contracture, trabeculations with cellules, and many small diverticula. A cysto-aerogram presented many scattered diverticula, the largest of which was 2 cm. in diameter. Excretory urography revealed nonvisualization of the pelvis, calyces and ureter on the left. The urine was cloudy and contained many white and red blood cells. Treatment was conservative and consisted mainly of palliative measures plus sulfadiazine.

Case 2. No. 34486, 1945, Kings County Hospital, E. W., a 36 year old woman complained of white urine, nocturia and sporadic bouts of hematuria for a period of 3 months. Her past history revealed previous treatment for diabetes mellitus. Cystoscopic examination presented an injected mucosa, 3 plus trabeculations with cellules, and a large diverticulum at the dome of the bladder. Multiple diverticula were seen on cystogram while a retrograde pyelogram revealed normal filling of the left calyceal system and poor visualization of the calyces of the upper and lower poles of the right kidney. The urine was cloudy, contained numerous mucus shreds and showed 2 plus albumin and 4 plus sugar. Treatment included sulfadiazine with palliative measures.

[1] Eisendrath, D. N. and Rolnick, H. C.: Urology. Philadelphia: J. B. Lippincott, 1930.
[2] Herman, L. The Practice of Urology. Philadelphia: W. B. Saunders Co., 1938.
[3] Schacht, F. W. and Crenshaw, J. L.: J. Urol., **24:** 393–410, 1930.
[4] Kutzmann, A. A.: Urol. & Cutan. Rev., **38:** 634–39, 1934.
[5] Kutzmann, A. A.: Am. J. Surg., **29:** 102–114, 1935.

Case 3. No. 12676, 1946, Kings County Hospital, J. M., a 24 year old woman, was admitted with symptoms of dysuria, terminal hematuria, dyspareunia and suprapubic pain of several days' duration, since the return of her husband from an overseas station. Her past history revealed two cesarian sections, the last one 5 years prior to admission. A diverticulum, with its opening lying proximal to the right ureteral orifice, was observed on cystoscopy. Pelvic examination revealed inflammation about the external urethral meatus and a tender introitus and cervix. Sulfadiazine therapy resulted in alleviation of all complaints.

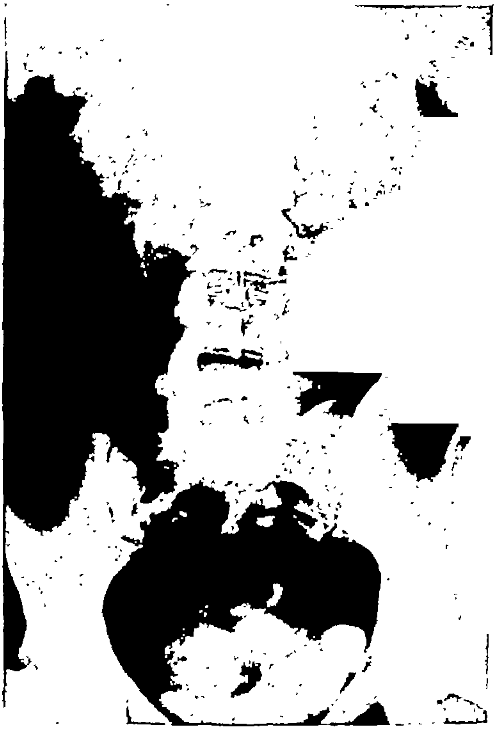

Fig. 1. Case 5. Normal excretory urogram also showing diverticulum of bladder

Case 4. No. 11623, 1946, Kings County Hospital, N. F., a 72 year old woman, complained of pain in the left side of 3 months' duration, accompanied by frequency, nocturia and burning. Cystoscopy revealed an edematous mucosa with 2 plus trabeculations and cellules. A moderate number of diverticula, 4 cm. in diameter, were seen by cystogram. Excretory urography revealed dilatation and irregularity of the renal pelvis and calyces of the right kidney. Treatment consisted of rest and penicillin.

Case 5. No. 30185, 1946, Kings County Hospital, G. Q., a 29 year old woman, was admitted with complaints of severe headaches and tenderness in the left costovertebral angle for 9 days. Several years prior to admission she had sporadic attacks of hematuria. Two years prior to admission, an appendectomy and left oophorectomy were performed. Cystoscopy revealed a contracted bladder neck and a diverticulum above the left ureteral orifice. Cysto-aerogram revealed a non-emptying diverticulum about 2½ to 3½ cm. in diameter, while an excretory urogram was negative (figs. 1 and 2, *A* and *B*). Urinalysis revealed many red blood cells and pus cells. A suprapubic cystostomy was performed with resection of the orifice of the diverticulum by a cutting loop and resection of the bladder neck with a punch. Penicillin and sulfadiazine were valuable adjuncts. Two weeks after surgery, a cysto-aerogram revealed complete emptying of the diverticulum. (fig. 2, *C* and *D*). At this same time, she was free of symptoms. The urine was negative.

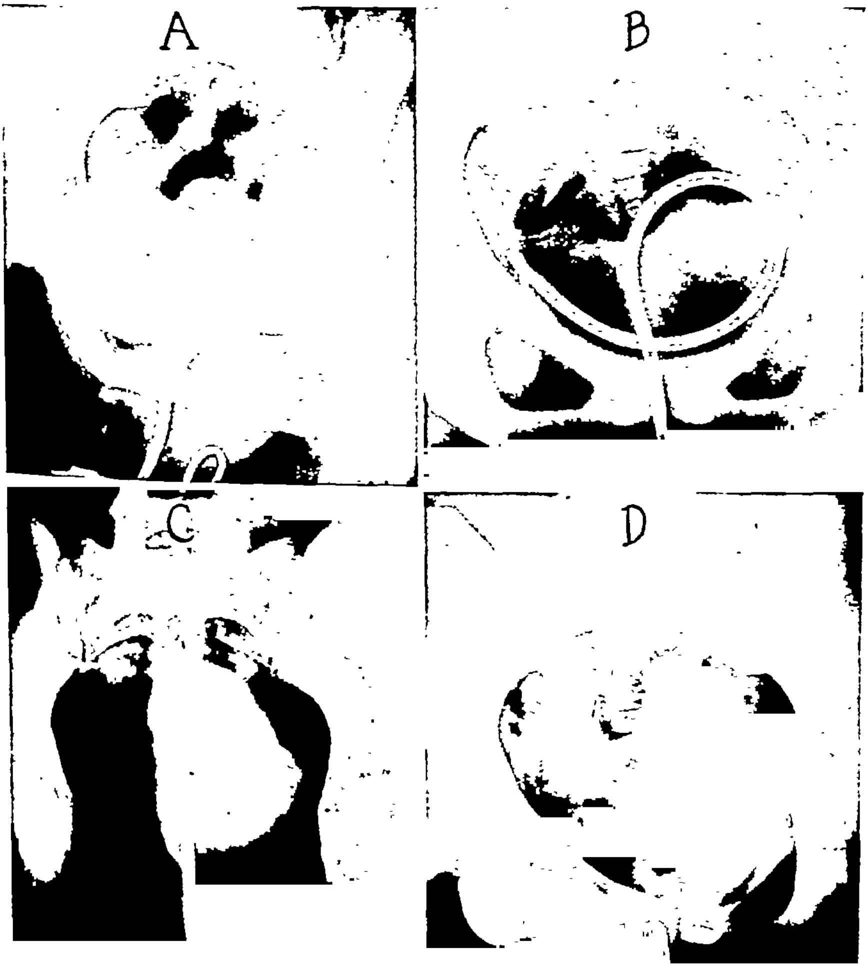

Fig. 2. Case 5. *A*, cystogram. Note diverticulum on left. *B*, cysto-aerogram revealing retention diverticulum. *C*, postoperative cystogram. Diverticulum is present. Ureters are visualized from excretory urogram taken prior to cystography. *D*, postoperative cysto-aerogram. Diverticulum has completely emptied.

Case 6. No. 17930, 1946. Kings County Hospital. J. P., a 65 year old woman, entered the hospital because of urinary incontinence of 1 year's duration, following a panhysterectomy. The opening of a diverticulum in the midline was seen cystoscopically, behind an hypertrophied interureteric ridge. Methylene blue inserted into the bladder appeared in the vagina although the vesical end of the fistula could not be seen with the aid of a cystoscope. The bladder neck was normal. Excretory urography was negative. The patient refused surgery.

DISCUSSION

It is generally agreed that bladder diverticula may be congenital or acquired, or a combination of both. Many congenital diverticula are symptom-free and therefore remain unrecognized to be discovered only when symptoms referable to the urinary tract occur; case 3 is an example. Except for the urethritis which brought the patient to the hospital, her diverticulum would not have been recognized. Jennings[6] cites an example in a 46 year old woman whose first attack of cystitis at that age led to the discovery of a true congenital diverticulum. In two of the remaining 5 cases of our series, no note was made as to etiology. In 3 patients, the diverticula were due to contracted bladder necks, and an hypertrophied interureteric ridge. Wershub,[7] Kutzmann, and others conclude from their cases that urethral caruncle, chronic granular urethritis, and urethral strictures are causes of acquired bladder diverticulum in the female.

From a study of the upper urinary tract in our series, it is apparent that the majority of vesical diverticula occur in association with upper urinary tract disease. Cases 1, 2 and 4 were complicated by kidney disease. While case 5 had a normal pyelogram, the patient nevertheless had clinical pyelonephritis. The prognosis in these cases depends on the extent of damage in the bladder, the kidneys and ureters resulting from infection and back pressure. There is no fixed therapeutic regimen. True congenital diverticula that are asymptomatic obviously require no treatment. Nonretentive diverticula may be treated conservatively by use of the appropriate antibiotics. Retentive diverticula require both the chemotherapeutic and antibiotic drugs plus surgery. Open operation is often used for both diverticula and fibrotic bladder necks. In case 5, a cure was effected by open surgery. Coming into more common use is the resectoscope for transurethral resection of a contracted bladder neck, for incision of the orifice of a retentive diverticulum, and for incision of an hypertrophied interureteric ridge.

SUMMARY AND CONCLUSIONS

Six cases of bladder diverticula in the female are presented and discussed. Studies of the upper urinary tract should be performed for possible renal and ureteral disease.

144 Joraleman St., Brooklyn 2, N. Y. (F. L. S.)
19 Schermerhorn St., Brooklyn 2, N. Y. (J. J. B.)
1858 Northern Blvd., Manhasset, N. Y. (S. H. R.)

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[6] Jennings, F. B.: Am. J. Surg., **52**: *107–110*, 1941.

[7] Wershub, L. P.: Am. J. Surg., **16**: 275–278, 1932.

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VESICAL NEOPLASM PROLAPSING THROUGH THE URETHRA AND SUGGESTING PRIMARY VAGINAL CARCINOMA

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Prolapse of urethral mucosa in women is a commonly recognized entity. Cases in which ureterocele presented through the urethra also have been recorded. Prolapse of a vesical neoplasm through the urethra is uncommon, however; cursory review of the literature for the past fifteen years failed to disclose such a case.

REPORT OF CASE

An unmarried woman 70 years old first came to the Mayo Clinic on February 14, 1951, complaining of "seepage from the vagina." A brownish vaginal discharge had necessitated her wearing pads for two years prior to her visit to the clinic. On the day before her admission she noticed that three pads had been saturated with bright red blood. Her only complaints referable to the urinary system were mild dysuria and frequency during the week preceding her visit to the clinic. She said she had not had hematuria.

In the past the patient had noted mild exertional dyspnea, and had been told that she had hypertension. She was taking iron for anemia.

Physical examination disclosed a senile woman. The blood pressure, in millimeters of mercury, was 190 systolic and 108 diastolic. The heart was somewhat enlarged to the left. The thyroid gland was nodular but only slightly enlarged. Pelvic examination was not entirely satisfactory because of tenderness and a nulliparous introitus, but a large, fungating, polypoid tumor was noted, apparently arising from the anterior wall of the vagina.

Urinalysis revealed erythrocyturia of grade 1 and pyuria of grade 2 (20 cells per field) in the voided specimen. The value for hemoglobin was 13.4 gm. per 100 cc of blood. The erythrocyte sedimentation rate was 32 mm. in one hour (Westergren method), and the value for urea was 40 mg. per 100 cc. A smear of vaginal secretions, taken for study for possible malignant cells, was reported to be unsatisfactory.

It was the impression of the gynecologist that the lesion represented a primary carcinoma of the vagina. However, in view of the relative infrequency of this lesion in comparison with the frequency of secondary vaginal malignant processes, it was considered advisable to carry out additional examination with the patient under the influence of anesthesia. A thorough pelvic examination was to be done, a specimen from the mass was to be taken for biopsy and dilatation and curettage were to be performed. With the patient anesthetized with nitrous oxide and pentothal sodium, vaginal examination disclosed, instead of a vaginal tumor, a prolapsing tumor with its stalk coming from the urethral meatus. The stalk was pulled out of the orifice as far as possible, clamped, ligated and divided. The tumor was 2 by 2 by 1 cm. Microscopically, it was found to be a transitional cel epithelioma, grade 3 (on the basis of 1 to 4) (fig. 1).

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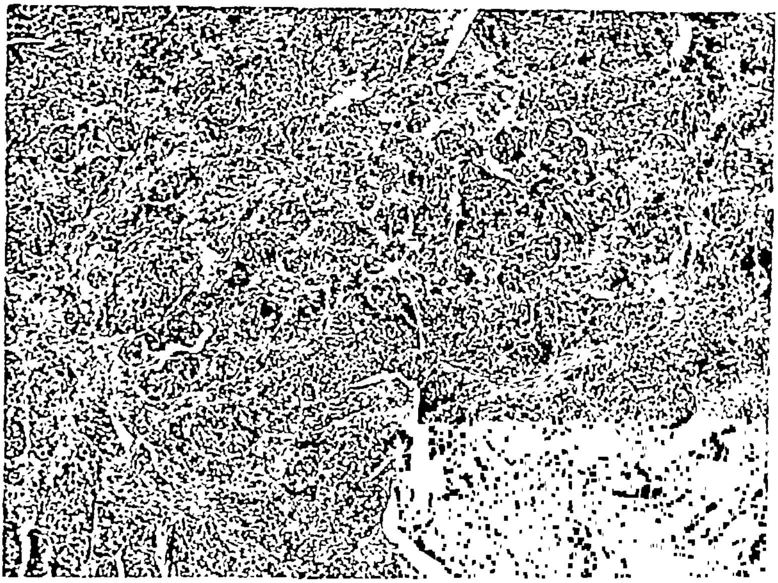

Fig. 1. Transitional cell epithelioma, grade 3 (hematoxylin and eosin, ×54).

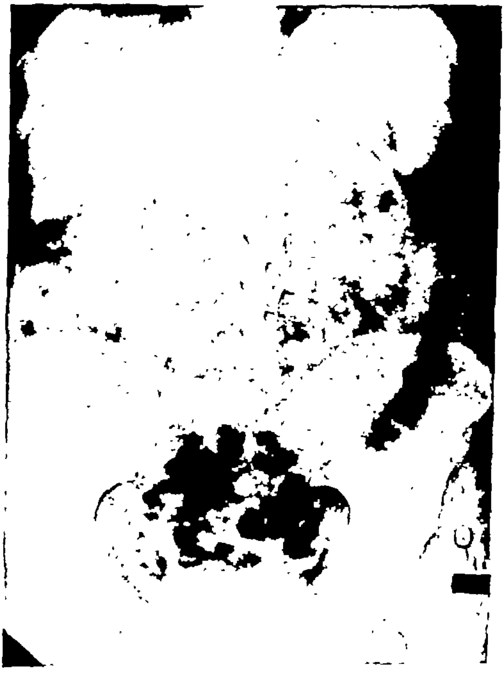

Fig. 2. Mild hydronephrosis on right, as disclosed in excretory urogram.

On the day after this procedure considerable gross hematuria developed, wi the passage of clots. A Foley bag catheter was inserted in the bladder and ur logic consultation was requested. At cystoscopy, after the evacuation of clots, the pedicle of a broad-based tumor was seen situated near the region of the right ureteral orifice. Since the orifice was not visualized, it could not be determined whether the pedicle was adjacent to the orifice or actually extending from it. The pedicle was excised with the resectoscope, and the area was thoroughly fulgurated. Microscopic examination of the pedicle revealed a transitional cell epithelioma of grade 3. An excretory urogram was not entirely satisfactory because of gas in the bowel, but it demonstrated good renal function bilaterally, with no evidence of obstruction. The remainder of the patient's stay was uneventful. She was dismissed 6 days after operation, and was advised to return at intervals for re-examination of the urinary tract.

The patient returned to the clinic for follow-up studies four months after her initial visit. She had no symptoms suggestive of recurrence of tumor. Urinalysis revealed erythrocyturia of grade 1 and pyuria of grade 1 (6 cells per field) in a catheterized specimen. Excretory urography disclosed pyelo-ureterectasis, grade 2, on the right side (fig. 2). Results of cystoscopy were negative in respect to recurrence of tumor. The right ureteral orifice appeared cicatricial, and attempts to catheterize it were unsuccessful. However, forceful spurts of urine were seen to be coming from it. In view of the absence of symptoms or evidence of recurrence, it was felt that no treatment was indicated. The patient was dismissed and advised to return in 6 months.

Six months later the patient returned for a second follow-up examination. She had continued to be free of symptoms. Examination of a catheterized specimen of urine disclosed erythrocyturia of grade 2, with only an occasional leukocyte per field with the high-power objective. Results of examination of the urinary tract by excretory urography and cystoscopy were similar to those obtained at the previous visit. Hydronephrosis on the right persisted, but there had been no progression of this process in the intervening six months. There was no cystoscopic evidence of recurrence of tumor. The right ureteral orifice still could not be catheterized, but a forceful jet of urine was again seen coming from it. The patient was dismissed, and is to be examined periodically in the future.

SUMMARY

A woman 70 years old had a pedunculated vesical neoplasm originating near the right ureteral orifice and prolapsing through the urethra, thus simulating a primary vaginal carcinoma. The lesion was treated by transurethral removal and fulguration of its base. At the time of this report the patient has been examined periodically within the ten months since treatment and was free of symptoms. Repeated cystoscopic examinations disclosed no recurrence of the vesical neoplasm.

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SEGMENTAL RESECTION AND RADIUM IMPLANTATION IN THE TREATMENT OF CARCINOMA OF THE URINARY BLADDER

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During the period from 1925 through 1949, a total of 2,273 cases of tumor of the urinary bladder were admitted to the Presbyterian Hospital and the Squier Urologic Clinic. These cases included all types of bladder tumors in various stages of development. Of the above total, 347 cases of carcinoma were treated by segmental resection or radium implantation at some time while they were under observation at this hospital. One hundred ninety-eight were treated by radium and 149 were treated by segmental resection. The two methods of treatment under consideration are alternate approaches to the primary treatment of certain types of early carcinoma of the bladder.

These cases were analyzed to ascertain which of the two methods provides the longest time interval free of disease, and to discover the particular indications for one or the other of these two methods.

In addition, we feel that these 347 cases should be evaluated from the standpoint of their survival rate. The treatment of many of these patients was not limited to segmental resection or radium implantation. Over a period of years they received one or more forms of therapy as clinically indicated while they were followed in our clinic. Therefore, though this is a selected group, the survival for each year and the cumulative survival rate by years has been calculated because it is a more meaningful expression of our effectiveness against a specific carcinoma than merely the cumulative survival rate at the end of five years.

The remaining cases were treated by cystoscopic fulguration or excision, by suprapubic fulguration or excision, by external x-ray therapy or by total cystectomy. Since carcinoma of the bladder is notoriously chronic and recurrent, individual patients often require several types of treatment in the course of their disease.

PART I

The decision to do a segmental resection or implant radium needles was based on the size, the location, the number of tumors present and the invasiveness of the tumor as far as could be determined by the appearance and palpation at the time of operation. The microscopic pattern varies greatly in a single lesion, making the preoperative biopsy of little value in planning treatment. However, *all cases in this series were proved by biopsy.* In the early cases in our series, the choice of the method was often based on whether the lesion was in a resectable area. Radium was used in the more inaccessible and more invasive types of tumors. The extent of microscopic invasion, a paramount aid in formulating the prognosis, can be determined in specimens resected at operation. This cannot be done when radium is implanted. Successful treatment by any method is dependent on the degree of differentiation of the tumor, on the knowledge of how far the tumor has extended beyond local barriers, and the total excision of the lesion or the application of adequate therapy which will cause its destruction.

Classification of cases based on these factors has been done previously.[1, 2, 3, 4, 5] The majority (80 per cent) of bladder tumors arise in the region of the trigone.[2] Solitary, pedunculated lesions are controlled most readily by any accepted method of treatment. Sessile and submucosal nodular lesions tend toward invasiveness, making eradication more difficult. Extensive lesions within the bladder offer mechanical difficulties to treatment and only those confined to a resectable area, or within reach of radium needles are amenable to either method of treatment. In the series reported by Lenz, Cahill, Melicow and Donlan,[4] lesions greater than 25 square cm. show higher incidence of recurrence. Based on the depth of penetration, Jewett and Strong[3] classified their cases in three divisions ranging from superficial to complete penetration through the bladder wall. However, despite preoperative biopsy studies, the actual depth of penetration is difficult to estimate unless the wall is resected. This is not always practical.

Comparison of the two methods. Our 347 cases have been classified in palliative and definitive groups based on the gross pathology at the time of operation. Palliative cases included all lesions greater than 25 square cm. and all lesions which had penetrated through the bladder wall. In a case with multiple tumors, if all the lesions were not implanted with radium the case was classed as palliative; the other lesions may have been fulgurated or excised. Also considered to be palliative were lesions which extended into the urethra beyond the reach of radium needles, and cases in which metastasis was apparent at operation.

The definitive group included cases in which the tumor had invaded the wall of the bladder but which had not penetrated through it. Lesions which involved the internal meatus but which did not reach down the urethra proper were deemed definitive for radium treatment. Lesions extending into the ureter were considered surgically definitive only when the entire neoplasm was resectable.

In the group treated by segmental resection (table 1), forty-six were classed as palliative, one hundred and three definitive. Nine of the operable cases were admitted after 1946 making them ineligible for five year evaluation, leaving 94 cases subject to analysis.

In the group treated by radium implantation, 91 cases were classed as palliative, 107 definitive. Of the latter, 44 were treated after 1946, leaving 63 cases to be evaluated on the basis of a five year survey.

In comparing the two groups for efficiency of treatment, the conclusions

[1] Herger, C. C. and Sauer, H. R.: Am. J. Roentgenol. & Rad. Ther., 47: 909-915, 1942.

[2] Jacobs, A.: Symposium: Carcinoma of the bladder. I. Treatment of cancer of the bladder by radium. Brit. J. Radiology, 22: 393-398, 1949.

[3] Jewett, H. J. and Strong, G. H.: Infiltrating carcinoma of the bladder: Relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J. Urol., 65: 366-372, 1946.

[4] Lenz, M., Cahill, G. F., Melicow, M. M. and Donlan, C. P.: Treatment of cancer of the bladder by radium needles. Am. J. Roentgenol. & Rad. Ther., 58: 486-491, 1947.

[5] Riches, E. W.: Symposium: Carcinoma of the bladder. II. Some further aspects of treatment. Brit. J. Radiology, 22: 398-402, 1949.

based not on survivals but rather on the longest time interval that the patients were free from clinical evidence of disease. Hence, any case was classed as a failure when a recurrence developed, even though the recurrence was successfully treated by another method. Also, all cases lost to follow-up were classed as failures at the time they were lost. It should be pointed out that in both surgical and radium groups analyzed in table 2 the percentage lost was the same, and relatively small, being approximately 10 per cent. However, since all patients lost were considered dead of disease, the figures given represent minimal clinical arrests.

Comment. Table 2 reveals that at any yearly period a higher proportion of persons remain clinically free of disease if the cancer of the bladder was treated by radium implantation rather than segmental resection. This is especially significant because radium was usually used on the more inaccessible and more invasive lesions. However, both treatment groups are small in number and therefore, the possibility must be considered that our better results with radium might be due to chance. Statistical analysis reveals that the higher per cent of 5 year clinical arrests in the case of radium implantation differs significantly from that of the segmental resection group—this despite the fact that the radium cases were frequently more invasive and more inaccessible. Therefore, it would appear that patients in whom either segmental resection or radium implantation is possible, would be better treated initially by radium implantation. This applies to all lesions under 25 square cm. which are of the sessile or submucosal nodular type, and to all lesions which biopsy reveals to be a grade 2, 3 or 4, especially if the excised specimen removed at operation reveals muscle invasion. The low grade malignant character of some grade 1 lesions is well known and perhaps these too should be similarly treated, particularly if only a portion of the lesion was obtained for microscopic study at the time of cystoscopic biopsy.

TABLE 1

	RADIUM IMPLANTATION	SEGMENTAL RESECTION	TOTAL
Definitive	107	103	210
Palliative	91	46	137
Total	198	149	347

Distribution in palliative and definitive groups of 347 cases of carcinoma of the bladder treated by segmental resection or radium implantation from 1925 through 1949.

TABLE 2. *Absolute clinical arrests*

Years after diagnosis	0	1	2	3	4	5
Segmental resection	94	50	36	28	25	21 (22.3%)
Radium implantation	63	43	34	30	26	24 (38.1%)

The above table sets forth the absolute clinical arrests at the end of each year after diagnosis of the 94 cases treated by segmental resection before 1946. It also compares these cases with the absolute arrests of 63 cases treated by radium implantation. These are definitive cases. Cases which developed recurrence and those which were lost to follow-up were classed as failures.

Exceptions to the rule are immediately apparent. There are cases in which a tumor occurs in the vertex of the bladder whose wall is extremely thin. Radium implantation can be technically difficult in such a location. Also, if there are multiple, widely scattered polypoid lesions, implantation may not be technically practical. Fulguration or excision would seem to be the treatment of choice. However, the possibility of treating multicentric cancers by a point source centered in the bladder by a Foley catheter as reported by Friedman[6] should be mentioned. Theoretically, this appears superior to the use of the intravesical bag filled with soluble radioactive materials. The possibility of rupture of the bag always exists with the attendant grave danger of radioactive contamination. Furthermore, the relation between the surface dose and depth dose in the bladder wall is relatively poor when compared to a single, centralized radium source because of the low penetrating power of beta rays. In addition, a large quantity of the beta emitter is necessary because little radiation from the radioactive material in the central part of the bag reaches the surface. Finally, though calculation of the tissue dose delivered by the soluble source is possible, it is much more difficult than the simple dosage calculation of a point source of radium.

Lastly, radium should not be used in cases of adenocarcinoma of the urachus. Here, wide segmental resection of the vertex and dissection of the atrophic urachus is the proper procedure.

PART II. ANNUAL AND CUMULATIVE SURVIVAL RATES OF 347 CASES OF CARCINOMA OF THE URINARY BLADDER

These patients were selected for study from all the cases of bladder carcinoma because at some time in the course of their disease there was clinical indication for segmental resection or radium implantation. Because carcinoma of the bladder is a chronic, recurrent disease, many of the cases under consideration received other forms of treatment either before or after radium insertion or segmental resection. Many required repeated fulguration or excision; some were treated by segmental resection after radium insertion or vice versa; a few eventually were treated by total cystectomy and some were given palliative external x-ray therapy. Some of these patients were treated by a number of these methods as suggested by the clinical course.

Excluded from this present series were those cases which on admission were obviously palliative from the clinical standpoint and so received neither segmental resection or radium implantation, and those early grade 1 lesions which received fulguration or excision only.

The usual method of tabulating results of treatment is the 5 year survival rate, but we believe this system is inadequate. It does not utilize all the available information about all the patients with a specific carcinoma at a particular clinic, such as the cases treated as recently as one, two or three years. It disregards prolongation of life in treated cases of specific cancers which do not survive five years but which would not have lived even two or three years if untreated. Any cumulative survival rate per se disregards the fact that some forms of *untreated* cancer have a considerable five year survival rate. Thus, to estimate completely the effect of treatment, a cumulative survival rate of *treated* cancer must compare with the corresponding cumulative survival rate of the same cancer *untreated.*

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[6] Friedman, M. and Lewis, L. G.: A new technic for radium treatment of carcinoma of the bladder. Radiology, 53: 342-352, 1949.

Lees and Lees[7] point out that a complete cure in many of these chronic tumor cases is an assumption. They also believe that the standard used in reporting the results must be easily understood and in a form that can be duplicated by others. Such a standard is duration of life, or delay in dying. It is a valuable index in assessing the effect of treatment of cancer. All cases can be included in the survey regardless of the period of observation. Furthermore, duration of life expressed as the annual survival rate permits a determination of the number of survivals in the largest number of patients at any given time after onset or diagnosis.

In calculating the cumulative survival rate by years, it is first necessary to determine the annual death rate. For this purpose we need for each follow-up year the number of living patients, the number known to be dead and the number last observed alive. The latter, about whom information is lacking after that year, includes those cases lost to follow up and those who, because of recent admission, could be observed only to a given year. We have assumed that the death rate of this uncertain group is the same as that of the known group. We have also assumed that the patients withdraw more or less uniformly throughout the year so that the number of withdrawals is exposed to the risk of dying for only half the year on the average. This is equivalent to only half their number being exposed to the risk of dying the entire year. The number of cases exposed to the risk of dying for the year is thus the number beginning the year less one-half of the withdrawals last observed alive that year. All these factors are expressed in the formula in table 3.*

Using this formula, the cumulative survival rates from the onset of symptoms of 347 cases of tumor of the bladder treated by several methods as required by the clinical considerations is determined. The cumulative survival rate for each year has been computed and entered in the last column of table 3. For any particular anniversary this is obtained by multiplying the annual survival rates through that year. Thus, the three year survival rate in our series is 86.2% × 80.8% × 88.0% and equals 61.4%. The ten year survival rate is obtained in a similar manner, i.e., by multiplying the annual survival rate of each of the ten years, and equals 27.1%.

The cumulative survival rate of 347 cases has been plotted along with those of 28 cases of untreated cancer of the bladder reported by Welch and Nathanson.[8] Both rates are dated from onset of symptoms.

Figure 1 shows that the treatment of carcinoma of the bladder, whether initially considered definitive or palliative, prolongs life. Three years after the onset

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* The authors gratefully acknowledge the help of Dr. John W. Fertig, Professor of Biostatistics, School of Public Health of the Faculty of Medicine, Columbia University, New York.

[7] Lees, J. S. and Lees, T. W.: Numerical estimation in cancer and cancer treatment. Cancer, 3: 377–409, 1950.

[8] Welch, C. E. and Nathanson, I. T.: Life expectancy and Incidence of malignant disease. IV. Carcinoma of the urinary tract. Am. J. Cancer, 31: 586–597, 1937.

TABLE 3. *Annual survival rates of 347 treated cases of tumor of the bladder from onset of symptoms*

YEARS AFTER ONSET	NUMBER PRESENT AT BEGINNING OF YEAR	NUMBER LIVING LAST OBSERVED DURING YEAR	NUMBER DYING DURING YEAR	NUMBER LOST TO FOLLOW-UP DURING YEAR	EFFECTIVE NUMBER PRESENT DURING YEAR	PROBABILITY OF DYING DURING YEAR (ANNUAL DEATH RATE) %	PROBABILITY OF SURVIVING THROUGH THE YEAR (ANNUAL SURVIVAL RATE) %	CUMULATIVE SURVIVAL RATE BY YEARS %
x	l_x	w_x	d_x	a_x	$l_x - \frac{1}{2}(w_x + a_x)$	q_x	$100 - q_x$	
0–1	347	0	47	19	337.5	13.9	86.2	86.2
1–2	281	5	52	18	269.5	19.2	80.8	69.8
2–3	206	6	24	6	200.0	12.0	88	61.4
3–4	170	15	13	6	159.5	8.2	91.8	56.4
4–5	136	5	19	7	130.0	14.6	85.4	48.0
5–6	105	5	12	1	102.0	11.7	88.3	42.4
6–7	87	1	13	2	85.5	15.2	84.8	36.0
7–8	71	5	6	2	67.5	8.8	91.2	32.8
8–9	58	6	3	0	55	5.4	94.6	31.0
9–10	49	2	5	2	47	10.6	89.4	27.1
10+	40							

In the first column, years after onset is represented as x, and in the second the number present at the beginning of the year as l_x; w_x represents the number of the uncertain group last observed during the year because of recency of admission; a_x indicates the number lost to follow-up during the year. The number dying during the year is d_x. Thus, $l_x - \frac{1}{2}(w_x + a_x)$ expresses the effective number exposed to the risk of dying during the year. The number dying or d_x divided by the effective number present during the year gives q_x, which is the per cent dying during the year. The annual death rate is deducted from 100% to obtain the annual survival rate. The annual survival rates are then successively multiplied to obtain the cumulative survival rate in the last column.

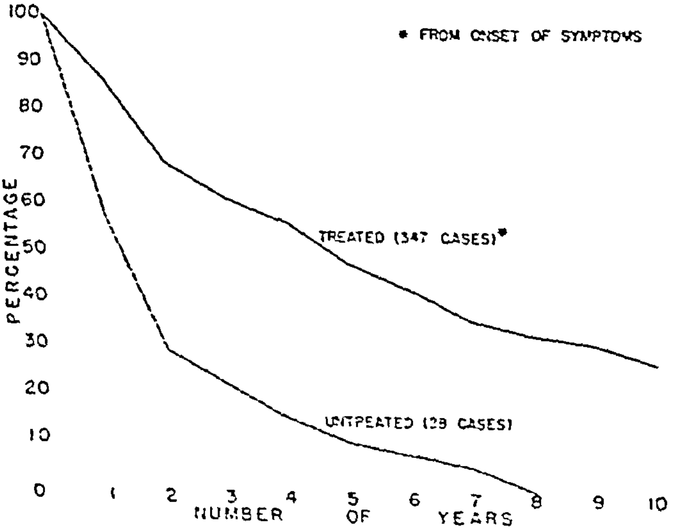

FIG. 1. Comparison of the cumulative survival by years of 347 cases of carcinoma of the bladder treated by several methods as clinically indicated, with a group of untreated cases reported by Welch and Nathanson.[1] Both curves are calculated from onset of symptoms. Treatment of carcinoma of bladder appreciably prolongs life.

of symptoms, 61.4 per cent are alive in the treated group as compared to 22 per cent in the untreated group. At 5 years 48.0 per cent are alive if treated as opposed to only 10% in the untreated group. At 8 years, 32.8 per cent are alive if treated, while Welch and Nathanson[8] state that the last untreated patient died eight years after onset of symptoms.

Figure 2 compares the normal life expectancy* of our particular group of patients if they had not developed cancer of the bladder with their actual survival rate dated from time of diagnosis. The degree to which carcinoma of the urinary bladder shortens life is apparent.

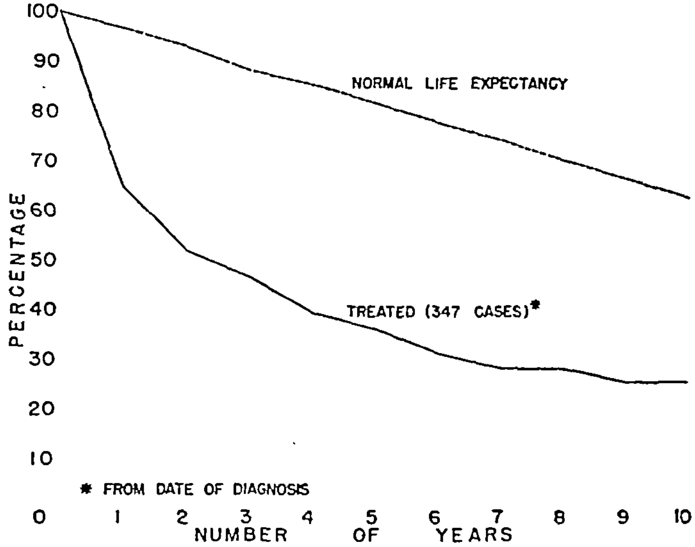

FIG. 2. Cumulative survival by years of 347 cases of bladder is plotted from date of diagnosis. It is compared with normal life expectancy of 347 patients of similar age calculated from the United States Life Tables. This graph shows that carcinoma of bladder shortens life in spite of treatment.

COMMENT

In calculating the cumulative survival rate by years of a large number of urinary bladder carcinomas treated by several proved methods utilized by urologic surgeons and radiotherapists, it has been found that life is prolonged. When the yearly survival of these treated cases is compared with untreated cases (fig. 1) the salutary effect of treatment is readily apparent.

As previously stated, carcinoma of the bladder is a chronic, recurrent disease. The physicians interested in the control of this cancer, the urologist, the radiologist and the chemotherapist must pool their knowledge and efforts in the treatment of any particular case. Decision as to treatment should be arrived at by consultation of these specialists after they have examined the patient together. The urologist has several methods of treatment to use as indicated. The radiologist has radium, radon, external x-ray therapy and isotopes, each with its indication. These therapists want the patient to remain alive for the longest possible time and with a minimum of symptoms. Clinical cure of cancer more properly should be considered clinical arrest. If in the life of a carcinoma of the bladder the patient averages 1, 5, 10 or 30 days of hospitalization and/or disability a year, but lives in comparative comfort or better the remainder of the time, this is successful treatment. Many diseases other than cancer are only controlled and never really cured. Some of them require more days of hospitalization and kill the patient in a briefer span of years than some cancers. As examples may be mentioned heart disease, kidney disease, arthritis and tuberculosis.

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* Calculation is based on the United States Life Tables (1929–1931).

Lastly, with the co-operation and combined decision of all interested physicians in each case, we should discard the expressions "surgical failure" and "radiation failure" in the control of cancer. We should substitute the idea of increased comfort and prolongation of life. Failure to accomplish either of these objectives is a failure of all of us to control cancer.

SUMMARY

A higher percentage of patients with carcinoma of the bladder are clinically free of disease at any given time following radium implantation than a similar group treated by segmental resection.

Therefore, radium implantation is recommended as the initial treatment in patients with grade 2 or more malignant, polypoid lesions and in submucosal nodular and sessile lesions.

The treatment of carcinoma of the bladder is a combined undertaking in which urologist and radiologist cooperate, each administering various techniques of treatment in the course of the disease as indicated in the individual patient.

The cumulative survival rate by years is a better expression of our ability to arrest cancer and is superior than the five year survival rate commonly used.

Comparison of the cumulative survival rate by years in our 347 cases with untreated cases reveals that treatment of cancer of the bladder appreciably prolongs life.

The assistance of Dr. Samuel P. Marshall and Dr. Noble S. Maluf is gratefully acknowledged.

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THE RELATION OF THE PREOPERATIVE ESTIMATE TO THE PATHOLOGIC DEMONSTRATION OF THE EXTENT OF VESICAL NEOPLASMS

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The depth of penetration of the vesical wall by a primary neoplasm has a significant bearing on prognosis. Accordingly, knowledge of the extent of a vesical neoplasm would be valuable to the clinician who must decide on therapy. How accurately can the depth of invasion be determined before open operation or autopsy? Would a classification of vesical neoplasms according to clinical stages be sufficiently correct to have value?

Jewett and Strong[1] have shown a close correlation between the depth of penetration of the vesical wall by a primary neoplasm and the theoretical prognosis, based on an exhaustive study of autopsy material. Colby and Kerr[2] have pointed out that simple cystectomy provided only a 10 per cent 5-year survival if the vesical muscle had been invaded; if the muscle was not invaded, the various complications of such extensive treatment as cystectomy, made the results less favorable than those obtained by simpler means. Jewett, in particular, has stressed the value of bimanual pelvic examinations in the estimation of the extent of a vesical neoplasm. The cystoscopic evaluation has long been a major item in the decision as to type of therapy. Grading of the malignancy of neoplasms according to histologic characteristics once seemed to be the key to prognosis and treatment, but grading has lost its pre-eminence (due to a variety of factors, not the least of which is the considerable variation among pathologists and their individualized criteria). Dean[3] reported that the histologic grade of malignancy found on biopsy was lower than that found in the totally removed bladder in approximately one-half of the cases. However, it is important to know that careful attempts to obtain extensive and particularly deep biopsies were not always made in this series. Milner[4] found a close agreement between the grade derived from carefully and deeply made biopsies with the resectoscope and the grade derived from partial or total cystectomies. Of course, the roentgenographic findings characteristic of metastases or extensive invasion are overwhelmingly significant when clearly present; but the absence of these findings does not reliably exclude the existence of such spreads.

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[1] Jewett, H. J. and Strong, G. H.: Infiltrating carcinoma of the bladder: Relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J. Urol., 55: 366–372, 1946.

[2] Colby, F. H. and Kerr, W. S.: Carcinoma of the bladder. An evaluation of total cystectomy and other methods of treatment. New Eng. J. Med., 244: 504–506, 1951.

[3] Dean, A. L.: Comparison of the malignancy of bladder tumors as shown by the cystoscopic biopsy and subsequent examination of the entire excised organ. J. Urol., 59: 193–194, 1948.

[4] Milner, W. A.: Transurethral biopsy: An accurate method of determining the true malignancy of bladder carcinoma. J. Urol., 61: 917–923, 1949.

One hundred and four consecutive radical cystectomies have been carried out on patients with vesical neoplasm at the New York Hospital-Cornell Medical Center and the Memorial Center for Cancer and Allied Diseases. In each procedure the entire contents of the pelvis were removed to the best of our ability except that the rectum was left in place in 51 patients. Thus the bladder, prostate or vagina, the perivesical fat, the pelvic peritoneum, the internal genital organs, the pelvic nodes, and often most of the perineum, were removed. Certainly, ample material for a study of the local extent of the neoplasm was obtained. The pathologic data in these cases were carefully reviewed with the help of Drs. F. W. Stewart and J. M. Pearce, pathologists to the Memorial and New York-Cornell Centers.

A selection of patients for this radical procedure was made. In general, those with preoperatively demonstrable metastases outside the pelvis and those with very low grade lesions were not chosen. Actually, 4 had nodal metastases above the bifurcation of the aorta which it seemed possible to remove, so the operation was carried out. Also there were 12 patients with histologically low grade neoplasms who received this treatment (because of multiple rapid recurrences, a change in histologic picture, etc.). It is evident, therefore, that a representative cross-section of small low-grade neoplasms and of neoplasms already extensively metastasized is not present in this series. Most important however, a representative cross-section of moderate-to-large and fully malignant neoplasms probably is represented, since we were not deterred from carrying out these extensive procedures on account of unfavorable associated disorders. During this period open exploration revealed grossly inaccessible cancer three times and in only these three was the operation abandoned. Finally, the conditions of this study are those of clinical practice: that is, those of living patients as they presented themselves rather than terminal results obtained from post-mortem examinations.

A classification of vesical neoplasms according to their physical extent was necessary for this study—and indeed seems desirable for general use in order to permit accurate comparisons between reported series. The first category chosen was that of invasion of the muscle because there is general agreement that this is a distinctly unfavorable sign.[1, 2, 5] The stage for muscle penetration was labelled 'stage B'. There are theoretical grounds as well as some actual experience to indicate a notable difference, prognostically and therapeutically, between superficial and deep involvement of the muscle.[6] Accordingly, stage B was divided into two parts at the mid-level of the muscle; B_1 and B_2 representing superficial and deep penetration respectively.

Neoplasms superficial to the muscle were made into two stages—O and A. In stage O are those growths limited to the mucosa, including the simplest papillomas and intra-epithelial (in situ) carcinomas. It occasionally happens that a biopsy demonstrates a neoplasm yet the pathologist fails to find it in

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[5] Flocks, R. H.: Treatment of patients with carcinoma of the bladder. J. A. M. A., 145: 295-301, 1951.

[6] Jewett, H. J.: Discussion. J. Urol., 65: 846, 1951.

the specimen from the definitive operation. On first thought such a situation would appear invariably as a gross error and mismanagement. In our experience these examples have consisted of cases in which low-grade growths, particularly those with multiple rapid recurrences and changing histology, have been extensively treated but a wider removal has then been decided upon. In other words, proof of the existence of neoplasm still existed yet no neoplasm was found in the more extensive specimen. A 30-day time limit was set between the biopsy showing neoplasm and the later specimen in which neoplasm was not found. One would certainly not wish to assume a vesical tumor cured on the basis of a 30-day follow-up. Brevity and the purposes of this presentation do not permit a discussion of the justification, or lack of it, for extensive surgery in such cases; but it is evident that a stage should be made to include these examples because they do occur and yet the situation is not the same prognostically or therapeutically as with easily demonstrated growths. Accordingly, 'stage O', which means existence of neoplasm but without demonstrable spread beyond the mucosa proper, was chosen to indicate the simplest papilloma, intra-epithelial carcinoma, and those neoplasms proved present histologically within 30 days preceding the definitive surgery yet not found in the full specimen.

Stage A was delineated for neoplasms which involve the submucosa but extend no farther.

Stage C was defined as involvement of the perivesical fat or even the capsule of adjacent organs but no farther. If the substance of an adjacent organ is involved, not only is the tumor vigorous and quite extensive but new possibilities for further spreads appear. Adherence to, or even the involvement of the capsule or serosa of an adjacent organ does not constitute invasion of the substance of that organ: thus, neoplasm in the prostatic urethra would not place the lesion in a greater stage than 'C' unless the neoplasm is shown to have passed the confines of the urethra proper and entered the true prostatic substance at a depth below the urethral structures.

Again theoretically, hope can be entertained that radical surgery might even cure a few patients who had metastases or invasion of the substance of adjacent organs. However, that hope is dim indeed if the neoplasm has spread beyond the confines of the bony pelvis. Accordingly, 'stage D', where the neoplasm is beyond the limits of the bladder and perivesical fat, was divided into two sections: namely, 'D_1' and 'D_2'. In D_1 the lesion is still within the pelvis, including the invasion of the pelvic walls or the recti muscles below the level of the umbilicus. In other words, the lesion in D_1 was considered to be below the sacral promontory, medial to the psoas muscles, and not beyond the perineum externally below. In stage D_2 the neoplasm was beyond the limits of the pelvis and thus included the cases of distant metastases, metastases in lymph nodes external to the inguinal ligament and in nodes above the sacral promontory. The sacral promontory and the bifurcation of the aorta are not at the same level and the lower limit was chosen arbitrarily to make stage D_1 a slightly smaller category.

This system provides four main stages in the physical extent of vesical neoplasms with the divisions along easily recognized morphologic lines. Stages B and D are readily subdivided as described if such should be considered advisable. In general terms, stage O indicates limitation to the mucosa; stage A, limitation to not beyond the submucosa; stage B to not beyond the muscle; stage C, the fat; and stage D, metastases and massive invasion of adjacent structures.* These stages are illustrated diagrammatically in figure 1.

In a period of possible transition one hesitates to drop the old for the untried new. Grading of the malignancy of neoplasms, with all its inadequacies, is known to have practical significance. As mentioned earlier, really satisfactory biopsies are necessary as no pathologist can do better than the quality of the material with which he is supplied. No tumor is better than its worst part. In the past we employed a system of histologic grading composed of: papilloma, papilloma with atypical cells, and then grades 1 to 4 of malignant neoplasm or cancer. In a large series of cases it could be shown[7] that these divisions did have general prognostic significance. Dr. Neil Beall reviewed a group of 277 cases in which the first biopsy at Memorial Hospital was reported as papilloma or papilloma with atypical cells. The incidence of subsequent cancer was approximately twice as great in the group with atypical cells as in that of pure

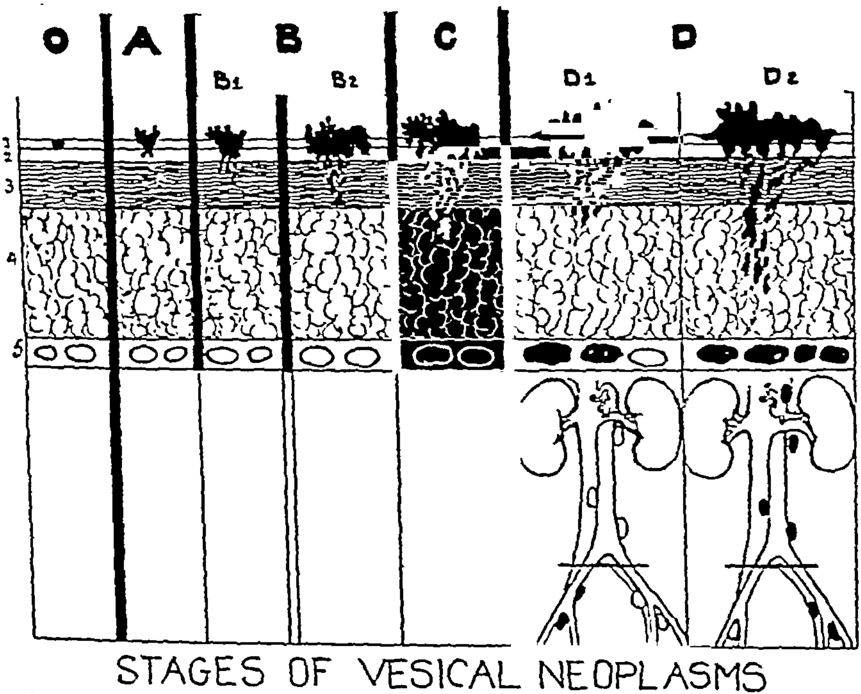

FIG. 1. 1 = mucosa; 2 = submucosa; 3 = muscle; 4 = fat; and 5 = lymph nodes

papilloma. However, from a practical point of view uniformity might be facilitated and confusion reduced by consolidating papilloma and papilloma with atypical cells as one grade, termed, 'papilloma'; grades 1 and 2 carcinoma into 'low grade carcinoma'; and grades 3 and 4 into 'high grade carcinoma'. Unusual neoplasms, such as sarcoma, could merely be labelled as such.

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* Helpful suggestions regarding the labels for the different groups were given by Dr. Hugh J. Jewett.

[7] Marshall, V. F.: A comparison of radiation and surgery for cancer of the bladder. J. A. M. A., 134: 501-507, 1947.

In this manner, a dual classification resulted, consisting essentially of 4 stages and 3 grades. In a fashion, the tested old and the theoretical new were combined. Perhaps experience will permit greater simplification, even to the extent of dropping grading. Just now however, the duality would seem to serve a purpose since there is some relation between stage and grade as will be shown. If, for example, a series of unselected neoplasms was reported as containing papillomas in stages B, C, or D, there would be a grave doubt as to reliability. In the other direction, a large percentage of high grade carcinomas found to be in stage O would suggest that the grading system used was most liberal and possibly valueless. It can be noted in table 4 that, in general, as the stage (demonstrated in the laboratory) increases so does the histologic grade.

TABLE 1

Clinical stage = O, A, and B_1 (29 caes)
- 19 were found to be stage O, A, or B_1 (66%)
- 10 were found to be stage B_2, C or D (33+%)

Clinical stage = B_2, C, and D (75 cases)
- 10 were found to be stage O, A or B_1 (13%)
- 65 were found to be stage B_2, C, or D (87%)

Of 104 cases, 84 or 81% correctly estimated relative to half-muscle level
Of 104 cases, 20 or 19% incorrectly estimated relative to half-muscle level

All preoperative findings were carefully reviewed in each case of this series, and the lesions classified in clinical stages before reviewing the gross and histologic findings of our pathologists. The records were surprisingly detailed in this regard, although hardly ideal. The influence of Jewett's work had been felt and all of us realized that sooner or later some study like this was inevitable. All the available preoperative findings were used to judge the clinical stage. Cystoscopy, bimanual palpation, and roentgenography were the principal diagnostic procedures relied upon, the biopsy report and the history being relegated to minor roles for the purpose of this investigation. Continued interest and further experience might improve the accuracy of these preoperative estimations.

In view of the aforementioned tendency to consider superficial neoplasms as probably curable and those deeper as probably incurable, it seemed particularly desirable to assess our ability to judge preoperatively whether the dividing line of the half-way level in the muscle had been passed. When we had estimated clinically that the lesion was relatively superficial (that is, in stage O, A, or B_1), careful study of the specimen showed that we were correct in 19 out of 29 cases, or 66 per cent; and, wrong in 33 per cent (table 1). When we considered clinically that the neoplasm had passed this division (that is, to be in stages B_2, C, or D), we were correct in 65 out of 75 cases, or 87 per cent; and wrong in 13 per cent. Accuracy was therefore greater if the lesion was judged to have infiltrated deeply. However, the growths thought preoperatively to be in the lesser stages were a highly select group, a group chosen for surgery because of unusual features in the illness. On the other hand, those estimated to be in stages B, C, and D_1, are nearly a representative cross-section (short of generalized carcinomatosis) of fully developed malignant neoplasms. Considering the entire series, 84, or 81 per cent were correctly catalogued; and 20, or 19 per cent were incorrectly placed in regard to the dividing line of the half-way mark in the muscle layer. Since the largest component of this whole series consists of deeply infiltrating cancers which notoriously extend even farther than routine pathologic study may demonstrate, the probability is that the actual error has been less than these figures show. On the whole, these findings were surprisingly better than had been anticipated.

TABLE 2

Clinical stage = O (0 cases)
Clinical stage = A and B_1 (29 cases)
5 were pathologically stage O
14 were pathologically stage A or B_1
7 were pathologically stage B_2 or C
3 were pathologically stage D

Clinical stage = B_2 and C (67 cases)
0 were pathologically stage O
9 were pathologically stage A or B_1
25 were pathologically stage B_2 or C
33 were pathologically stage D

Clinical stage = D (8 cases)
0 were pathologically stage O
1 was pathologically stage A or B_1
2 were pathologically stage B_1 or C
5 were pathologically stage D

From table 2 the gross deviation of each clinical stage from the pathologic stage is recorded. The spread is fairly great and most errors were in underestimating the extent of the neoplasm (as might be expected considering the selection of patients as described). Forty-three or 42 per cent were pathologically in a stage greater than the clinical appraisal (that is, clinically underestimated). Seventeen cases or 16 per cent were pathologically in a stage less than that of the clinical appraisal (clinically overestimated). Forty-four or 43 per cent were found to have the same pathologic stage as that estimated preoperatively.

In table 3 the same deviations are shown, but with further details according to the degree of histologic malignancy. As might be expected, the lesions of low-grade neoplasia were judged to be in the lesser stages more accurately than if a high-grade lesion was judged to be in a lesser stage. In other words, if the clinical evidence indicated a low stage and really adequate biopsy shows a high grade of malignancy the chance for serious error (underestimating the extent of the lesion) is considerable. For example, only one-fourth of the high-grade neoplasms which were thought clinically to be in stage A or B_1 were actually in stage A or B_1; rather, they were likely to be in the more extensive stages. On the other hand, if the clinical stage was A or B_1 and a good biopsy revealed only low-grade carcinoma or papilloma, accuracy was surprisingly high (only 1 out of 17 was pathologically in a greater stage than estimated clinically). Accuracy was better in clinical stage B_2 and C when the lesion was of high grade malignancy, but even so a really significant number of high-grade lesions were clinically underestimated (i.e. pathologically in a greater stage). The clinical stage D group is too small to warrant other than recording in the table.

TABLE 3

Clinical Stage = A and B_1 (29 cases)
11 were pathologic stage A or B_1, and were low grade
3 were pathologic stage A or B_1 and were high grade
3 were pathologic stage O and papilloma
2 were pathologic stage O and low grade
1 was pathologic stage B_2 and low grade
6 were pathologic stage B_2 or C and high grade
3 were pathologic stage D and high grade
—
29

Clinical stage = B_2 and C (67 cases)
None were papilloma
2 were pathologic stage B_2 or C and low grade
21 were pathologic stage B_2 or C and high grade
4 were pathologic stage A or B_1 and low grade
4 were pathologic stage D and low grade
5 were pathologic stage A or B_1 and high grade
28 were pathologic stage D and high grade
2 were pathologic stage B or C and myosarcoma
1 was pathologic stage D and myosarcoma
—
67

Clinical stage = D (8 cases)
None were papilloma
0 were pathologic stage D and low grade
5 were pathologic stage D and high grade
1 was pathologic stage B_1 and low grade
2 were pathologic stage B_2 or C and high grade
—
8

A tabulation of the 104 cases is presented (table 4) showing the subdivisions of the stages as well as the detailed steps of grading formerly used. It can be noted that grading does have a relation to stage, albeit not absolute. Studying the listings suggests strongly that a few errors might have been avoided by the clinician if he had been more influenced by the grade obtained from an adequate biopsy.

TABLE 4

Clinical Stage = *O* (No cases)

Clinical stage = *A* (7 cases)

Pathologic stage was O, and papilloma in	2
Pathologic stage was O, and Grade II in	1
Pathologic stage was A, and Grade III in	1
Pathologic stage was B_1, and Grade I in	1
Pathologic stage was B_2, and Grade III in	1
Pathologic stage was D_1, and Grade III in	1
	7

Clinical stage = B_1 (22 cases)

Pathologic stage was O, and papilloma in	1
Pathologic stage was O, and Grade II, in	1
Pathologic stage was A, and Grade I, in	5
Pathologic stage was A, and Grade II, in	3
Pathologic stage was A, and Grade III, in	1
Pathologic stage was B_1, and Grade II, in	2
Pathologic stage was B_2, and Grade III, in	1
Pathologic stage was B_2, and Grade II, in	1
Pathologic stage was C, and Grade III, in	3
Pathologic stage was C, and Grade IV, in	2
Pathologic stage was D_1, and Grade III, in	2
	22

Clinical stage = B_2 (22 cases)

Pathologic stage was A, and Grade II in	1
Pathologic stage was B_1, and Grade III in	2
Pathologic stage was B_1, and Grade IV in	1
Pathologic stage was B_2, and Grade II in	1
Pathologic stage was B_2, and Grade III in	1
Pathologic stage was B_2, and Grade IV in	1
Pathologic stage was C, and Grade III in	3
Pathologic stage was C, and Grade IV in	2
Pathologic stage was D_1, and Grade II in	1
Pathologic stage was D_1, and Grade III in	5
Pathologic stage was D_1, and Grade IV in	3
Pathologic stage was B_2, and myosarcoma in	1
	22

Clinical stage = *C* (45 cases)

Pathologic stage was A and Grade I in	2
Pathologic stage was B_1 and Grade II in	1
Pathologic stage was B_1 and Grade III in	2
Pathologic stage was B_2 and Grade IV in	1
Pathologic stage was C and Grade II in	1
Pathologic stage was C and Grade III in	10
Pathologic stage was C and Grade IV in	3
Pathologic stage was D_1 and Grade II in	3

TABLE 4—*Continued*

Clinical stage = *C* (45 cases)	
Pathologic stage was D_1 and Grade III in	9
Pathologic stage was D_1 and Grade IV in	7
Pathologic stage was D_2 and Grade III in	1
Pathologic stage was D_2 and Grade IV in	3
Pathologic stage was B_2 and myosarcoma in	1
Pathologic stage was D_1 and myosarcoma in	1
	45
Clinical stage = D_1 (7 cases)	
Pathologic stage was A and Grade 1 in	1
Pathologic stage was B_2 and Grade 3 in	1
Pathologic stage was C and Grade 3 in	1
Pathologic stage was D_1 and Grade 3 in	1
Pathologic stage was D_1 and Grade 4 in	2
Pathologic stage was D_2 and Grade 4 in	1
	7
Clinical stage = D_2 (1 case)	
Pathologic stage was D_2 and Grade III in	1

It is worth pointing out that in all instances in which the neoplasm was clearly to the right or left, the metastases to the nodes, when present, occurred on the ipsilateral side. Furthermore, from the size, distribution, etc. of these nodal metastases they appeared to have occurred on the ipsilateral side before the contralateral side in those cases in which there were bilateral metastases. Lesions near the midline, however, seem capable of metastasizing to either side, often to both. There was one instance in which a crossed metastasis appeared to have occurred, but a careful study of the record raises a strong suspicion that the words "right" and left" were confused in the pathologic report. In other words, when a contralateral metastasis did occur there were always more extensive ipsilateral metastases (with one possible exception as just mentioned.) These facts should not be taken to mean that exclusively contralateral metastases cannot occur, but such occurrence must be at least uncommon.

Only one instance of a nodal metastasis from a primary lesion which had not progressed beyond the half-way level of the muscle was found, and this patient had had a segmental resection eight months previously. In one case a nodal metastasis was found from a neoplasm which had barely passed the half-way level in the muscle.

SUMMARY AND CONCLUSION

A classification of vesical neoplasms according to the physical extent of the lesion and also according to the histological evidence of the degree of malignancy has been presented. In a series of 104 consecutive patients having radical cystectomy, the preoperative or clinical stage was compared with the postoperative or pathologic stage—the latter being based on study of the specimen removed.

The degree of accuracy in regard to whether or not the mid-portion of the muscle layer had been passed by the neoplasm was surprisingly great; that is, 81 per cent accurate. It has been pointed out that papilloma and low grade lesions and those in the least stages did not represent a true sampling of such lesions, but a true sampling of other more extensive and more malignant neoplasms was thought to be present (short of generalized carcinomatosis). The deviations in any single category were fairly marked, but from considering the histologic grading it seems highly probable that the process of clinical staging would be improved if really adequate biopsies were obtained and attention paid to the grade arrived at from their study. In this presentation the best pathologic material was used for the grading and no attempt made to compare preoperative and postoperative specimens as to grading, which has already been done by Dean and by Milner, and by others. The dual classification here presented appears to have value other than purely academic. The duality permits a partial check on the process of judging the clinical stages and also would seem to improve the comparability of different series. The final significance of these studies depends on the accurate follow-up of a significant number of patients in the various categories, although there are reports strongly suggesting that this classification may be prognostically significant. However, it can be seen that the physical extent of a vesical neoplasm can be judged with a significant degree of accuracy by careful attention to well-known diagnostic measures.

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ANALYSIS OF RESULTS OF PROSTATIC SURGERY IN 866 CASES

GEORGE BULKLEY AND JOHN W. KEARNS

The following is an analysis of 8 years of prostatic surgery, suprapubic and transurethral, done during the period from July 1942, through July 1950. All patients of this series were operated upon one of the services* at Wesley Memorial Hospital. During this period 142 suprapubic enucleations were carried out upon as many patients, and 724 transurethral resections were done upon 632 patients; making a total of 866 operative procedures upon 774 patients. Approximately ten per cent of the patients were from the clinics of Northwestern University Medical School (table 1).

The hospital records of each patient were studied in order to determine the incidence of diseases associated with prostatic disease causing vesical neck obstruction. These are enumerated in table 2.

Complications following each operative procedure were studied. In addition to hospital records, the office records of patients who were followed were utilized in order to include complications occurring after discharge from the hospital. Nearly all patients were followed for at least three months, and the majority for several years. Complications following suprapubic prostatectomy are listed in table 3. Those following transurethral resection are listed in table 4.

In 58 patients the procedure was repeated one or more times in order to obtain a complete and satisfactory tissue removal.

In the entire series there was a total of 23 deaths; 11 following transurethral resection and 12 after suprapubic enucleation (table 5).

The cause of death was accurately determined by autopsy in 18 cases. The remaining 5 cases are shown with probable cause of death (table 6).

The size of the prostatic tissue removed was determined from the weights given by the pathologist. The very few cases in which the specimen was not weighed were omitted from these figures which are listed in table 7.

DISCUSSION

This study was undertaken in order to evaluate the end results of prostatectomy done by suprapubic and transurethral routes. It has been our practice to choose the surgical approach which seemed best suited to each patient. In general, glands estimated to be over 50 gm. were usually selected for the suprapubic approach and those estimated to be smaller were handled transurethrally if there were no stone or diverticulum in the bladder. Cases done by perineal or retropubic approach were not included in this study.

The incidence of carcinoma of the prostate in this series was 10.8 per cent. Urinary tract calculi were the most frequent complicating factors in the urinary tract and may alter the surgical approach in order to insure their removal. Carcinoma occurring in the bladder and upper urinary tract must always be kept

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* The service of Dr. Vincent J. O'Conor, Dr. J. Kenneth Sokol and Residents (Dr. Edmund Crowley, Dr. Robert A. McAllister, and the authors).

TABLE 1

	OPERATIONS July 1942–July 1950	PATIENTS
Transurethral	724	632
Suprapubic	142*	142
Total	866	774

TABLE 2

Associated Genito-Urinary Conditions

Calculi	
Bladder	36
Prostatic	7
Ureteral	8
Renal	11
Bladder diverticulum (large)	22
Hydronephrosis	10
Carcinoma	
Prostate	83
Bladder	23
Kidney and ureter	4
Tuberculosis of prostate	1
Gumma of prostate	1
Pyonephrosis, left	1
Prostatic abscess	2
Preoperative urethral stricture	4
Renal insufficiency	1
Interstitial cystitis	1

Associated Conditions, Systemic

Cardiovascular disease	163
Cerebral vascular accident	8
Severe cardiac decompensation	8
Diabetes mellitus	32
Tabes dorsalis	15
Bronchial asthma	14
Emphysema (pulmonary)	12
Carcinoma	
Colon	9
Gallbladder	2
Larynx	1
Paget's disease	2
Pulmonary tuberculosis, active	1
Thyrotoxicosis	1
Rupture of gallbladder	1
Peptic ulcer	1
Hepatic cirrhosis	1
Pernicious anemia	2
Chronic lymphatic leukemia	1

in mind and looked for, especially in cases with postoperative bleeding where the prostate may be assumed erroneously to be the source. Hypertension, arterio-

TABLE 3. *Complications following suprapubic prostatectomy*

Hemorrhage (severe)	5 (2 fatal)
Contracture of vesical neck requiring added treatment	11
Pyelonephritis (severe)	4 (2 fatal)
Pulmonary embolism	5 (4 fatal)
Coronary occlusion	2 (1 fatal)
Cardiac failure	3 (3 fatal)
Pneumonia	4
Persistent suprapubic fistula (over three months)	3
Persistent urinary infection (low grade)	2
Epididymitis	3
Partial incontinence	2
Incisional hernia	1
Bladder calculi	1

TABLE 4. *Complications following transurethral resection*

Hemorrhage	
Cystotomy required for adequate control	11
Additional transurethral coagulation	30
Bag catheter pressure adequate for control	9
Extravasation of urine	5 (1 fatal)
Pyelonephritis (severe)	12 (2 fatal)
Myocardial infarction	5 (3 fatal)
Cardiac failure	3 (2 fatal)
Vegetative endocarditis	1 (1 fatal)
Epididymitis	33
Stricture of urethra and meatus	30
Persistent low grade urinary infection (over three months)	21
Partial incontinence of urine	8
"Atonic" bladder	5
Pulmonary embolism	4 (1 fatal)
Cerebral thrombosis	1 (1 fatal)
Phlebothrombosis	1

TABLE 5. *Mortality*

	DEATHS	% MORTALITY
Transurethral	11	1.4
Suprapubic	12	8.5
Total	23	2.66

TABLE 6. *Causes of death*

Pyelonephritis with uremia	4
Cardiac failure	4 (autopsy on 2)
Myocardial infarction	3
Pulmonary embolism	4
Hemorrhage	2
Carcinomatosis	1
Extravasation of urine	1
Cerebral thrombosis	1
Doubtful	3 (no autopsy)

sclerosis, and coronary heart disease were not considered as contraindications to surgery with proper medical management, although in many cases they definitely increased the risk.

The most serious complications following either type of surgery are seen to be those occurring in the cardiovascular system. This is undoubtedly due to the age group of these patients. Hemorrhage is seen to be the next most frequent serious complication. Bleeding of significant degree occurred quite frequently following transurethral resection but there were no cases where death was attributable to bleeding alone. It has been our practice to return the patient promptly to the operating room for inspection of the prostatic bed and coagulation of the bleeders through the resectoscope, rather than to attempt to control bleeding by catheter alone. In cases where this did not suffice, suprapubic cystotomy and suture or packing were done without delay with complete control of bleeding.

TABLE 7. *Size of gland*

	Gm.
Suprapubic	
Largest	200
Smallest	10
Average	64.4
Transurethral	
Largest	90
Smallest	1*
Average	14.1*

* This compilation makes no distinction between benign prostatic hyperplasia, vesical neck contracture due to fibrosis, median bar or small median lobes. Secondary and repeated tissue removals are also included in this figure.

Extravasation of urine following transurethral resection is a complication which must be constantly kept in mind. Those cases in which the extravasation was recognized promptly and where immediate cystotomy and adequate drainage was provided made a rapid and uneventful recovery. In one patient where adequate drainage was delayed death was the result of intraperitoneal extravasation and peritonitis.

The initial transurethral resection was not complete in 58 patients. Some of these operations were planned in two or more stages, due to the size of the gland or the desire to limit operating time because the patient presented as a poor operative risk. In a very few instances the procedure was not completed because of troublesome bleeding or systemic complications occurring during resection.

A few re-resections were done in patients in whom the operation was thought to be complete in the first instance but who did not regain good urinary function in a short period of time. A second procedure was then done without delay.

It has been our policy to re-examine all patients who have difficulty voiding or who fail to empty the bladder within the first 4 to 7 days following the removal of the catheter. These patients are re-examined with the resectoscope and any remaining obstructing tissue is removed about a week after the initial resection.

It is our belief that following an adequate resection, the majority of patients will void well without pain and will usually empty the bladder completely within a week or ten days.

Epididymitis occurred chiefly during a period when routine vasectomy was not done. Routine vasectomy is now done on all patients except the younger age group and epididymitis is a very infrequent occurrence. Stricture of the urethra occurs most frequently at the meatus and is prevented in many cases by adequate meatotomy at the time of surgery. Some patients were treated by meatotomy during the follow-up period. Stricture or contracture of the vesical neck following suprapubic prostatectomy occurred in 11 patients and was adequately treated by dilation with sounds in eight. Two patients had obstructing scar tissue removed by transurethral resection, and in one suprapubic cystotomy was repeated for intravesical removal of obstructing tissue.

The mortality figures show a considerably higher death rate following suprapubic prostatectomy. This is apparently due to the embolic and cardiac complications associated with the aftermath of a more major surgical procedure. The mortality following transurethral resection is comparable with that reported by other authors who have enjoyed a similar experience.

SUMMARY

A group of 866 patients undergoing prostatic surgery was reviewed in order to present our experience and in an effort to determine complications which might be avoided.

Study of these cases indicates that further efforts to reduce the mortality and morbidity should be directed chiefly to careful preoperative study and preparation of patients with significant cardiovascular disease.

In our hands, transurethral resection has been the safest procedure in these poor risk patients.

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PROGRESS IN SUPRAPUBIC PROSTATECTOMY

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The fundamental principles in the successful management of the patient with prostatic hypertrophy demand first, a thorough preoperative cystoscopic and rectal examination to determine the operative procedure most suitable for the relief of the obstructive process, and second, an adequate study of the patient's fitness to withstand the indicated operation.

Due consideration must be given to any co-existing vesical or systemic disease which may influence one's final decision and also deference must be paid to the preference and special proficiencies of the operator in those cases where any procedure might be used with equal prospect of an excellent result.

For the comparatively young man who at mid-life develops a large obstructive prostate gland at a time when he should have many useful years ahead of him both as a breadwinner and as a husband we have favored the suprapubic enucleation, because it nearly always gives us functional end results most gratifying to the patient and the prompt restoration to health equally gratifying to the urologist. We also like to stress this method in teaching since it permits the simultaneous correction of bladder lesions and its infrequent complications are easily controlled.

With the demand for hospital beds and the skyrocketing of the cost of hospitalization have come time saving factors. We use all that are applicable and can show a gratifying decrease in hospital days with no loss of safety to the patient.

The purpose of this paper is to compare statistically two series of patients, 27 each, who were submitted to suprapubic prostatectomy by urologic residents 13 years apart, in order to show progress in this short time period. The two techniques used have numerous variations although the basic method is the same. Advocates of the recently introduced retropubic operation have maintained that its principal advantage lies in the fact that the postoperative course is short and free of suprapubic drainage of urine. We shall show in this report that the simpler suprapubic method results in just as short a postoperative time with the added advantage of being technically easier to perform, and requiring less operative time.

The technique employed in the first group of cases to be reviewed from the period 1937–1938 involved the use of the bulky Pilcher bag and a large suprapubic drainage tube (fig. 1, *A*). After removal of these agents, a urethral catheter was introduced and tied in place. Urethritis, infected prostatic bed, and epididymitis often followed; days of blood stained urine were the rule; healing was slower; and hospitalization up to a month or longer occasioned little comment.

The detailed method used in the 1949–1950 series follows: While the patient is still in his room a 22F Foley catheter with 30 cc bag is inserted into the bladder. (Larger bags are used for very large glands.) After anesthesia has begun, the bladder is irrigated with silver nitrate solution 1:10,000 and filled with sterile water. Through a median hypogastric incision the bladder is exposed in the usual manner and the peritoneal fold reflected upwards. The bladder is opened and emptied by suction. The bladder wall is then thoroughly inspected using Deaver retractors. The tip of the Foley catheter is grasped with a curved Kelly hemostat, drawn up out of the wound, and held over the symphysis out of the way. The prostate gland is then enucleated after the method of Squier. Rectal counterpressure is used only if enucleation is difficult. A sponge on a long forceps is pressed into the prostatic cavity to control bleeding while the bladder neck is inspected. A modified Hartmann punch is used to remove any obstructing tissue or for cutting through a hypertrophied interureteric ridge or bar. An oxycel Foley cone is placed on the catheter as illustrated (fig. 1, *B*) and an initial 10 cc of

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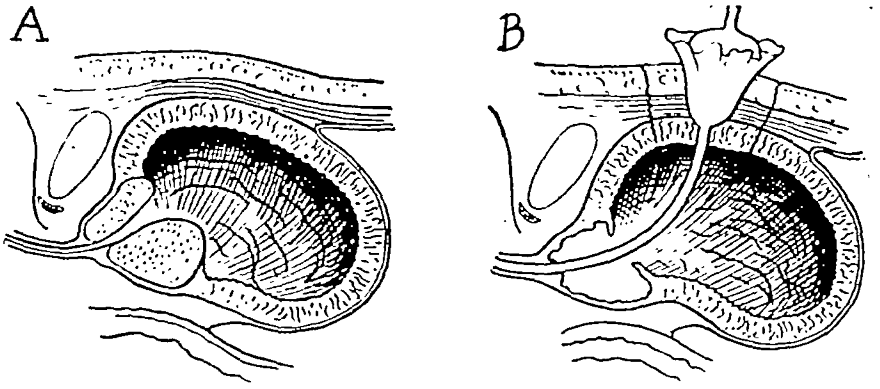
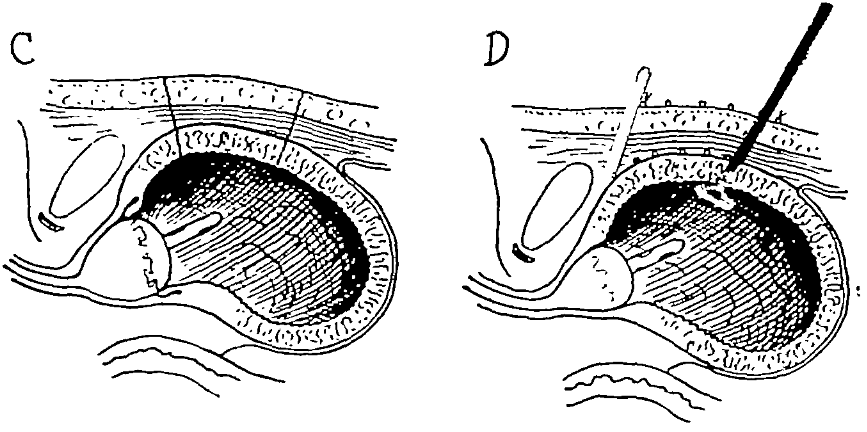
* Deceased



Hypertrophied prostate represented by lightly shaded area at base of bladder.

Following enucleation a Foley hemostatic catheter is inserted through the urethra. An Oxycel Cone is perforated with a forceps, slipped on to the catheter, and placed about the bag, which is then inflated.



Oxycel-covered Foley bag is drawn into the fossa to control bleeding from the prostatic bed. Later, inflation of the bag is reduced and finally the catheter is removed through the urethra.

Oxycel gradually disintegrates without interfering with healing of the wound. Bladder irrigations may be performed as usual.

FIG. 1. After Parke, Davis & Co.

water is placed in the bag. The catheter is then drawn down until the oxycel and partially inflated bag lie entirely within the prostatic fossa. The bag is then distended until it fills the prostatic bed, 20 cc additional water usually being added for this purpose. The bladder is then closed from below upward using No. 1 chromic continuous sutures through all layers of the bladder wall. An open end Pezzer catheter (22 or 24F) is placed in the upper end of the bladder wound and anchored as shown in figure 1, *B*. It is not sutured to the bladder. After placing a drain in the prevesical space the recti muscles are approximated with a few interrupted No. 1 plain cat gut sutures. The fascia is closed with continuous No. 1 chromic gut. The skin is closed with interrupted vertical mattress sutures of silk. Both the Pezzer catheter and drain are sutured to the skin using single silk sutures. Only such traction is used on the Foley catheter as may be necessary to keep it in the prostatic fossa for the control of bleeding.

Four hours postoperatively, traction is released and the bag is deflated until there is just enough fluid remaining to keep it indwelling, 5–10 cc being sufficient for this purpose. Irrigation is not used unless the tubes become blocked and then sterile water is forced gently through the Foley catheter and out the Pezzer catheter until drainage is free. Usually there is no fresh bleeding. The Pezzer suprapubic tube and prevesical drain are removed the following morning (about 18 hours postoperatively) and the urethral catheter remains in place 7 days. Each morning the bladder is gently irrigated to remove small collections of the disintegrating oxycel gauze. In case of a poorly draining catheter it may be replaced to prevent re-opening of the suprapubic wound. Smears and cultures of the urine are taken both pre- and postoperatively and the antibiotics of choice used promptly. Ambulation begins usually on the second or third day. The catheter is not clamped at any time even though the patient may be out of bed.

The first case summary illustrates a typical history of the series of 1937–1938.

A 76-year-old white man was admitted with symptoms of difficulty in urination and dysuria of 2 years' duration. The prostate was grade 2 by rectal examination and cystoscopy. Three ounces of residual urine were present.

Laboratory studies were negative. An internist said that the patient was a good surgical risk.

Suprapubic prostatectomy was performed, using a Pilcher bag and traction for hemostasis. A rubber drainage tube 1 inch in diameter was sutured to the upper angle of the bladder and brought out the lower angle of the wound alongside a one-half inch rubber tube drain placed in the space of Retzius. The wound was closed in layers. Traction was released in 5 hours and the bag emptied in 18 hours. The space of Retzius drain was removed on the second postoperative day, at which time an indwelling 24F Robinson catheter was inserted. On the eighth postoperative day unilateral epididymitis developed, necessitating removal of the urethral catheter until the twentieth postoperative day. The wound closed and the patient became dry suprapubically on the twenty-third day but a pinpoint leak developed on the twenty-ninth day. This was closed solidly by the thirty-fourth day when the catheter was removed and the patient was allowed out of bed for the first time. By the time of discharge on the forty-first day he was voiding with perfect control, without residual, and had regained sufficient strength to climb a flight of stairs without effort. Pathological diagnosis of the gland was "benign prostatic hypertrophy."

A typical average history taken from the 1940–50 series follows for comparison:

A 67-year-old Negro was admitted through the accident ward with acute urinary retention. Symptoms of three to four months' duration were diurnal and nocturnal frequency (6–8 times at night), difficulty in starting the stream and occasional dribbling. The prostate was graded 2 plus by both rectal and cystoscopic examination. A Foley catheter was inserted, obtaining 5 ounces of residual urine.

TABLE 1. *Comparison of statistics*

	YEAR	
	1937–38	1949–50
Total cases reported	27	27
Average age of patient	64.1	63.3
Average preoperative days	18.7	6.2
Average postoperative days	35.2	10.5
Average hospitalization days	53.9	16.7
First day dry	17th	2nd
Day of voiding	25th	7th
Complications:		
Incontinence	2 (mild)	0
Epididymitis	5	1
Peri-urethral abscess	1	0
Secondary hemorrhage	0	1
Wound breakdown	1	0
Cerebral accident	1	0
Coronary occlusion	1	0
Total:	11	2
Deaths:		
Pulmonary embolus	0	1
Coronary occlusion	2	1

The medical survey classed the patient as a good risk. The laboratory studies were negative except for a mixed urinary tract infection Gram positive and negative rods for which the patient was given gantrisin, 1 gm., q.i.d. and crysticillin, 300,000 units daily for 3 days preoperatively.

A suprapubic prostatectomy was performed using a No. 22 Foley 30 cc bag with oxycel cone for hemostasis. A 24F open end Pezzer catheter was used for suprapubic drainage and a Penrose drain placed in the space of Retzius as demonstrated in figure 1, *B*. The suprapubic Pezzer catheter was removed together with the space of Retzius drain 16 hours postoperatively. No suprapubic drainage followed their removal. The patient was ambulatory on the second day and the urethral catheter was removed on the morning of the seventh day. He voided well that day without residual urine and was discharged the next morning. He was seen in the clinic periodically for the next 2 months. The urine became clear within a month after discharge.

Table 1 reveals some interesting figures. Two groups of patients were evaluated with their age group being 64.1 years to 63.3 years. In the 1937 series the average preoperative hospital days were 18.7 compared with 6.2 in the recent group. In all the first series the large suprapubic tube was removed on the fifth postoperative day leaving a sinus that filled in slowly while in the second series, the small suprapubic tube was removed on the first postoperative day and the tissues promptly closed. The postoperative time of urethral catheter drainage averaged 25 days in the older series compared with 7 days in the new group. Complications such as epididymitis were reduced from 25 per cent to 4 per cent and the average postoperative days from 35.2 to 10.5 which is very significant in these days of crowded hospitals.

It is our belief that the improvement in results may be explained by eight points: 1) the use of small tubes; 2) earlier release of tension on the urethral bag; 3) earlier removal of all tubes; 4) the use of antibiotics; 5) the use of the Foley catheter bag in place of the Pilcher bag; 6) oxycel gauze as a hemostatic agent; 7) routine transfusions and indicated intravenous therapy; 8) early ambulation.

CONCLUSIONS

A comparison of methods is presented to show progress in suprapubic prostatectomy.

Results of comparable series of cases done by resident urologists in the years 1938 and 1949 are presented.

There has been a steady trend towards shorter hospitalization of the patient.

The antibiotics and improved methods of drainage and hemostasis have decreased the incidence of morbidity in suprapubic prostatectomy.

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EVALUATION OF CURRENT TREATMENT OF PROSTATIC CANCER

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Prostatic cancer is a problem of increasing importance. Fifty years ago Richard Wolff was able to collect only 83 cases from the world literature. Today we know from routine autopsy studies that at least 14 per cent of men over 50 harbor this disease in one form or another.[1] Using this figure, Hinman has calculated that there are in this country today 3,000,000 men over 50 with prostatic cancer,[2] which makes it the most common malignancy in the aging male.[3] Among all men dying of cancer, Smith[4] found it to be exceeded only by cancer of the stomach and bowel. By careful study of a series of 50 consecutive prostates obtained from men over 50, Baron and Angrist[5] found carcinoma in 23, or 46 per cent. Although this figure relates to occult cancer, its potential significance cannot be ignored. With life expectancy improving, the percentage of men eligible for clinical prostatic cancer is steadily increasing.

Early diagnosis is difficult. The disease is insidious, causing few symptoms until late in its course. At the time of the first examination in 90–95 per cent of patients, the malignant process is too advanced for surgically curative measures. In most cases where the growth is deemed potentially curable by radical surgery, the disease has been asymptomatic preoperatively, having been discovered quite by accident on routine rectal examination.

Progress has been made in the palliative treatment of patients with advanced, incurable disease. Largely as the result of the original contributions of Huggins and those working with him, most prostatic cancer patients now live more comfortably, and possibly longer, than their predecessors did in the pre-endocrine era. Today, with research in prostatic cancer proceeding at clinical and experimental levels in a number of institutions, the outlook for the future is hopeful.

The ultimate yardstick of the effectiveness of any form of therapy is its ability to cure the disease. In prostatic cancer, where the percentage of actual cures has been so low, it has been convenient to use comparative studies based on the ability of different methods of treatment to prolong life beyond the expectancy of untreated cases.

Such studies have approached the problem in several ways: 1) number of survivors, apparently without disease, after a specified period, usually 5 years;

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Damon Runyon Cancer Research Fellow.

[1] Rich, A. R.: J. Urol., 33: 215–23, 1935.

[2] Hinman, F.: J. A. M. A., 135: 136–41, 1947.

[3] Hinman, F.: Calif. Med., 68: 338–43, 1948.

[4] Smith, G. G.: J. Urol., 64: 671–80, 1950.

[5] Baron, E. and Angrist, A.: Arch. Path., 32: 787–93, 1941.

2) number of patients dead of the disease after a specified period, usually 5 years; 3) the average duration of life after diagnosis or institution of therapy.

The comparative merits of these methods need not be discussed at this time. It is pertinent, however, to point out that such studies, while of value in indicating trends, can be misleading, unless coupled with a thorough knowledge of the natural history of prostatic cancer. Unfortunately, this knowledge is only partially within our grasp today. The tendency to draw specious conclusions regarding absolute curability from analysis of a 5-year series is all too common today, and certainly to be deplored.

Before treating patients with prostatic cancer, it has been customary to classify them as either early or advanced, according to certain simple clinical criteria (table 1). In those cases where rectal examination is inconclusive, biopsy of the prostate must be resorted to. Sternal aspiration biopsy may also be of aid in doubtful cases.[6]

TABLE 1. *Classification of prostatic cancer*

I. Rectal examination
    a. Early—i.e. limited to the gland proper
    b. Advanced—i.e. beyond the gland proper

II. Bone x-rays
    a. Without metastases
    b. With metastases

III. Serum acid phosphatase
    a. Normal
    b. Elevated

EARLY PROSTATIC CANCER

It is generally agreed that radical perineal excision of the prostate, seminal vesicles and adjacent bladder neck is the treatment of choice when the cancer is confined to the prostate itself. This operation, first carried out by Young in 1904, was not hastily improvised, but was based on a thorough understanding of the pathogenesis of the disease. Modifications which ignore the fascial planes along which prostatic cancer spreads, and which do not remove intact the seminal vesicles and their fascia, the bladder neck and apex of the gland, fail in their purpose.

Jewett[7] has reviewed 222 radical perineal prostatectomies done at the Brady Urological Institute from 1904 to 1948 (table 2). Of 78 patients with cancer confined to the prostate on rectal palpation, 51.3 per cent lived 5 years or longer, without evidence of the disease. Of 43 with cancer confined to the prostate on rectal palpation, 28 per cent lived 10 years or longer, the maximum survival being 27 years. No patient who lived 10 years subsequently showed evidence of cancer. This is as close to an absolute cure as one can hope for.

Although Jewett found that the perineural lymphatics were frequently involved histologically, the 10 year figures show that distant metastases should not be inferred from this finding, as some have stated. This confirms Moore's statement in 1935[8] that, although perineural lymphatic infiltration occurs early in prostatic cancer, distant lymphatic invasion is a late phenomenon of the disease.

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[6] Alyea, E. P., and Rundles, R. W.: J. Urol., 62: 332-39, 1949.
[7] Jewett, H. J.: J. Urol., 61: 277-80, 1949.

Of great significance is the fact that the actual prostatic disease in Jewett's cases almost always exceeded the impression gained from rectal palpation. This finding points up the necessity for carrying out the operation as radically as possible, according to the principles described by Young. It also provides a rationale for the institution of endocrine treatment in all patients undergoing radical prostatectomy.[9, 10]

The applicability of the radical operation is, unfortunately, low. Patients must be good surgical risks, although the operative trauma is little more than that of a simple enucleation. It is doubtful whether patients over 70 should be subjected to the operation, in view of the limited life expectancy in older men. However, each case must be individualized. Jewett found the operation applicable in 11.2 per cent of all patients admitted with prostatic cancer to the Brady Urological Institute. This is higher than in most clinics, where figures run about 3–5 per cent.

TABLE 2. *Radical perineal prostatectomies, 1904 to 1948*

(From Jewett)

Total	222
Microscopically-proved prostatic cancer	190
Cancer limited to prostate on rectal examination	78
5 year closed series	78
Lived 5 years or longer	40 (51.3%)
10 year closed series	43
Lived 10 years or longer	12 (28%)

Operative mortality is low, about 3 per cent. Impotence follows radical prostatectomy in most, if not all, patients. The incidence of other postoperative complications is comparatively low, the most common one being urinary incontinence, which occurs in 12 per cent of patients.

OCCULT PROSTATIC CANCER

The treatment of clinically unsuspected, or occult, prostatic cancer discovered on subsequent histological examination after simple prostatectomy for apparently benign enlargement of the gland, has been the subject of debate recently. Hinman Jr. and Hinman[11] have reported a closed series of 14 patients discovered to have occult prostatic cancer after transurethral resection, and who were followed for at least 5 years (table 3). Five of these patients subsequently had radical perineal prostatectomies as well; their average survival was 67.8 months The comparable 5 year figure for the other 9, treated only with transurethral resection, was 36.8 months. On the basis of these data, these authors have recommended radical surgery as the treatment of choice for occult prostatic cancer.

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[8] Moore, R. A.: J. Urol., 33: 224–34, 1935.
[9] Colston, J. A. C. and Brendler, H.: J. A. M. A., 134: 845–53, 1947.
[10] Harrison, J. H. and Poutasse, E. F.: Am. J. Med., 11: 55–66, 1951.
[11] Hinman, F., Jr. and Hinman, F.: J. Urol., 62: 723–29, 1949.

Nesbit and Baum[12] have recently questioned this opinion. They have reported an analysis of 42 patients with occult prostatic cancer treated conservatively, i.e. by transurethral resection. Fourteen patients died of causes other than prostatic cancer. Two of the remaining 28 died of the disease, but the rest were alive and apparently well up to 12 years after the original diagnosis. Because of these figures, as well as the advanced ages of their patients, Nesbit and Baum doubt the necessity for radical surgery in patients with occult prostatic cancer.

As further evidence for their stand, Nesbit and Baum have drawn on a report by Thompson in 1942;[13] they state that he "reported a 60.9 per cent 5 year survival in 112 patients in whom clinically unsuspected adenocarcinoma was discovered following transurethral prostatectomy." A careful review of Thompson's article discloses that: 1) none of the patients in his series (887 in all) were considered as occult. In fact Thompson states clearly that all were diagnosed preoperatively as prostatic carcinoma. 2) The 112 cases cited by Nesbit and Baum from Thompson's report do not represent patients with occult cancer, but rather the number classified histologically as grade 1 (Broders). The term "occult" simply refers to cancer not suspected preoperatively; its histological grade of malignancy according to Broders (or any other method) may vary widely from relatively benign to extremely malignant. 3) The 60.9 per cent survival figure quoted by Nesbit and Baum alludes, not to the foregoing 112 patients, but only to 23 with grade 1 malignancies who were followed by Thompson for 5 years. Of these, 14, or 60.9 per cent were alive at the end of that time.

TABLE 3. *Occult prostatic cancer; 5 year closed series*

(From Hinman Jr. and Hinman)

Number discovered after transurethral prostatectomy	14
Treated with transurethral prostatectomy alone	9
Average survival	36.8 months
Treated with radical perineal prostatectomy	5
Average survival	67.8 months

Neither the Hinmans, nor Nesbit and Baum have presented convincing evidence in support of their arguments, primarily because neither series is large enough for statistical purposes. Although further data bearing on this question are extremely necessary before reaching a decision, it is possible at this time to approach the problem from certain logical considerations.

As stated previously, occult prostatic cancer may range widely in its degree of malignancy, as judged histologically. Similarly, there may be considerable variation in its inherent ability to grow and metastasize; unfortunately, we have no way of measuring this biological potential at present. Finally, despite its comparatively small size, as judged from our inability to diagnose it on rectal palpation, occult prostatic cancer may be early or late from the temporal standpoint.

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[12] Nesbit, R. M. and Baum, W. C.: J. Urol., 65: 890-94, 1951.

[13] Thompson, G. J.: J. A. M. A., 120: 1105-09, 1942.

We are, therefore, obliged to consider occult prostatic cancer simply as a form of carcinoma which is limited to the gland proper, and to treat it as such. Thus, it becomes mandatory at this time, and until convincing evidence to the contrary be submitted, that the patient with occult prostatic cancer be given the benefit of radical prostatectomy, providing, of course, that he be a suitable candidate from the standpoint of physical condition and life expectancy.

The frequency of occult prostatic carcinoma, with subsequent development of clinical cancer after simple prostatectomy, has led Smith and Woodruff[14] to recommend the use of total prostatectomy (without removing the seminal vesicles or a cuff of bladder) in selected cases with apparently benign enlargement of the gland. These observers advise it in those individuals who, because of symptoms, require an open operation, and in whom general condition, age and sexual habits offer no contra-indications. Further reports on the use of this procedure will be awaited with interest. The main objection to its adoption as standard practice is of course, the postoperative occurrence of impotence and urinary incontinence.

The use of the retropubic approach for radical prostatectomy has been reported.[15] The greatest disadvantage of this method is that the posterior aspect of the gland is inaccessible for biopsy under direct vision. Also, fascial planes cannot be identified as carefully as they can be from the perineal aspect. Finally, most observers agree that it is technically more difficult than the perineal operation.

ADVANCED PROSTATIC CANCER

The treatment of the patient with prostatic cancer which has spread beyond the immediate boundaries of the gland is no longer directed toward a cure, but, instead, is concerned with a limited, twofold objective: 1) relief of urinary symptoms, and 2) endocrine control of the tumor.

Transurethral resection has been the most widely used surgical method for dealing with the problem of bladder neck obstruction due to prostatic cancer. In the great majority of cases it has proved of great benefit. A certain number require multiple resections to cope with continued growth of the neoplasm. In a few patients marked irritability of the bladder and posterior urethra develops following transurethral resection. These people are better treated with permanent suprapubic cystostomy.[16]

The question has often been asked whether transurethral resection stimulates growth in the residual cancer. Many of us have seen occasional cases where the clinical course has suddenly taken a rapid turn for the worse after transurethral resection. Possibly this is post hoc reasoning. Flocks[16] has found no evidence to substantiate it. Nevertheless, because of such experiences, some individuals, notably Slaughter,[17] have completely abandoned transurethral resection in favor of cystostomy in those patients in whom the obstructive symptoms are not relieved by endocrine therapy.

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[14] Smith, G. G. and Woodruff, L. M.: J. Urol., 63: 1077–80, 1950.

[15] Memmelaar, J.: J. Urol., 62: 340–48, 1949.

[16] Flocks, R. H., Harness, W. N., Tudor, J. M. and Prendergast, L.: J. Urol., 66: 393–407, 1951.

For the treatment of the very large advanced cancer, open perineal or suprapubic resection of obstructing tissue has been favored by some. The results are said to compare favorably with those resected transurethrally, and the necessity for repeated operations is said to be obviated.

Endocrine measures alone are effective in certain instances in relieving the obstructive symptoms. Such cases, however, are in the minority, although there is some difference of opinion concerning this.

Some workers have attempted to widen the scope of the radical operation to include selected, nonmetastatic cases in which, on initial rectal palpation, the malignant process seems not to have extended very far beyond the immediate confines of the prostate. A certain number of these borderline advanced cases have responded so satisfactorily to endocrine therapy with respect to prostatic size, induration and degree of fixation, that radical prostatectomy has subsequently been undertaken in order to afford these patients the chance for a complete cure. It has also been stated that the operation is rendered easier technically by preliminary estrogen administration.[9] Scott and Parlow[18] have recently reported the use of this procedure in 22 patients, 13 of whom were followed for at least 3 years, all 13 being alive at the end of that time. Preoperative estrogens were given for an average of 15.6 months.

One of the early explanations for the seemingly beneficial effect of estrogen treatment in such cases was that it induced the prostatic neoplasm to recede from the marginal areas by depriving the more actively growing peripheral cells of necessary androgen, thus destroying them.[9] In the light of subsequent evidence this reasoning seems fallacious. Pathological examination of specimens removed by radical excision after estrogen administration has disclosed persistence of adenocarcinoma in extraprostatic structures.[9, 16] Furthermore, careful histological study has shown no tendency for increased cell destruction in peripheral areas as compared with the center of the neoplasm.

In view of the foregoing, grave doubts arise as to the value of preoperative endocrine therapy in these advanced cases. To begin with, as Jewett has shown,[7] it is quite likely that the malignant process will prove even more extensive histologically than pictured from rectal palpation. If we couple this knowledge with the histological proof that endocrine therapy does not completely destroy malignant cells situated in the extraprostatic tissues, there seems little reason to hope that we can transform an advanced cancer into one which is surgically curable, that is, capable of complete removal by Young's operation. Perhaps future studies will demonstrate the value of combined endocrine and surgical therapy in these borderline advanced cases. At this time, however, statistics are too meager to permit conclusions.

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[17] Slaughter, G. W.: Personal communication.

[18] Scott, W. W. and Parlow, A. L.: J. Urol., 65: 1093–1107, 1951.

The recent trend toward extensive pelvic surgery for the eradication of bladder cancer has prompted some workers to advocate complete prostato-vesiculocystectomy with pelvic lymph node dissection for selected cases of advanced prostatic cancer as well. In this connection the findings of Arnheim in 1948 are of interest.[19] In studying lymph node metastases from prostatic cancer in 176 autopsy cases, this investigator found the peri-aortic nodes most frequently involved, in about 49 per cent, and the iliacs in only about 34 per cent. Surprisingly, the tracheobronchial nodes were invaded almost as frequently as the iliacs, in about 27 per cent. These findings seem to contravene the desirability of pelvic node dissections in advanced cases.

ENDOCRINE TREATMENT

The palliative treatment of inoperable prostatic cancer by methods based on androgen control has proved one of the milestones in the continuing struggle to conquer this disease. Although no actual cures are on record, the recent survey by Nesbit and Baum[20] of the results of endocrine treatment of 1818 cases has shown an apparent increase in the percentage of 3 and 5 year survivors among treated cases, as compared with a series of untreated controls reported by Nesbit and Plumb in 1946.[21] This apparent improvement in longevity has been found in patients with or without metastases. The combination of castration and diethylstilbestrol has seemed to be most effective in the nonmetastatic group. In those with metastases, castration alone appears to have been as effective as combined therapy, so that it seems that estrogen administration has added little in the treatment of these cases. Further evidence of this is found in the metastatic patients treated with stilbestrol alone; their 5-year survivals have been only slightly more than the untreated controls.

In a careful analysis of these statistics, it is troublesome to note that, whereas *all* of the controls died of prostatic cancer, a considerable number of the treated cases (up to 33 per cent) died of other causes. It is not clear whether the latter were excluded from the actual survival statistics, as they certainly should have been. If, as it appears, they were included, then the results of the study are meaningless.

A few remarks are also in order concerning the validity of the control series employed in the above comparative study. These cases consisted of 795 patients seen prior to the advent of endocrine therapy; of this group 605 died of prostatic cancer. Those without evident metastases totaled 273; 90 per cent of this group were dead in 5 years. There were 231 with metastases, of whom 94 per cent were dead in 5 years. Of significance is the fact that 239, or about 40 per cent, of the 605 who died of prostatic cancer, *received no treatment whatsoever*. In view of the fact that patients receiving endocrine treatment today are also afforded the benefit of modern surgery, antibiotics and improved medical care, the validity of the above series for control purposes in a comparative study of endocrine methods of treatment may be seriously challenged.

At present, therefore, it may be stated that, although there is no question as

[19] Arnheim, F. K.: J. Urol., 60: 599–603, 1948.
[20] Nesbit, R. M. and Baum, W. C.: J. A. M. A., 143: 1317–20, 1950.
[21] Nesbit, R. M. and Plumb, R. T.: Surgery, 20: 263–72, 1946.

to the palliative value of existing endocrine measures in advanced prostatic cancer, no convincing proof is at hand that such measures will actually arrest the inexorable course of the disease. The need for adequate controls and treated cases, *selected without bias*, becomes a matter of incalculable importance in any attempt to evaluate the ultimate effectiveness of endocrine therapy.

TREATMENT OF RELAPSE

Despite initial improvement on endocrine treatment, the patient with advanced prostatic cancer inevitably suffers recurrence or reactivation of the malignant process. Whether the tumor has become "androgen-independent," or else insensitive to estrogens, is debatable.[22] Increasing the estrogen dosage to 1000 mg. daily or more may be of symptomatic benefit. Sometimes changing to another estrogen is helpful. TACE (tri-p-anisylchloroethylene), a synthetic estrogen, is currently being investigated in this regard.

The possibility that increased amounts of adrenal androgens are responsible for the relapse has led to the use of cortisone in an effort to inhibit the production of such androgens. Although cortisone does, in fact, suppress androgen secretion in female pseudohermaphroditism,[23] Thorn and Harrison have found that in patients adrenalectomized for hypertension, cortisone administration leads to an increase in urinary 17-ketosteroids, although not over preoperative levels.

The use of bilateral adrenalectomy in androgen control has recently been described by Huggins and Bergenstal.[24] Pituitary radiation has been reported to be of some benefit. Recently, however, Kelly and others[25] administered a pituitary tissue dose of 8,100–10,000 r to each of 3 female patients with advanced cancer. Autopsy studies disclosed no demonstrable changes in the tumors, metastases, pituitaries, or other endocrine glands. The use of hypophysectomy has recently been reported by Scott.[26]

It seems evident at this time that the endocrine treatment of prostatic cancer is more complicated than the anti-androgenic concept implies. Some patients with metastases actually benefit subjectively from testosterone,[27] although many develop a very prompt and severe relapse. Trunnell and Duffy[28] have obtained similar variable responses in patients with progesterone. The use of other "non-androgenic androgens" may yield valuable information.

Some work has been done with urethane, the nitrogen mustards and certain folic-acid derivatives. The results are not impressive. Radiation therapy has not been as widely used as in the past. However, recent work with intraprostatic injections of radioactive gold seems quite promising,[29] but is too early to evaluate.

[22] Deming, C. L.: J. Urol., **61:** 281-90, 1949.

[23] Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E.: Bull. Johns Hopkins Hosp. **86:** 249-52, 1950.

[24] Huggins, C. and Bergenstal, D. M.: J. A. M. A., **147:** 101-06, 1951.

[25] Kelly, K. H., Feldsted, E. T., Brown, R. F., Ortega, P., Bierman, H. R., Low-Beer, B. V. A. and Shimkin, M. B.: J. Nat. Cancer Inst., **11:** 967-83, 1951.

[26] Scott, W. W.: Address given before the Halsted Society, the Johns Hopkins Hospital, February 7, 1952.

[27] Brendler, H., Chase, W. E. and Scott, W. W.: Arch. Surg., **61:** 433-40, 1950.

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[29] Flocks, R. H.: Personal communication.

THE EVALUATION OF BIOLOGICAL POTENTIAL

For a fair comparison of different methods of treating prostatic cancer, it is essential that the disease be properly classified. It has been apparent to many observers that morphological criteria alone will not suffice, either gross or microscopic, whether based on extent of local spread, histological pattern, or degree of cellular differentiation. In most cases there is no correlation between the morphological appearance of the tumor and its behavior. Thus, we cannot predict the therapeutic response of a particular prostatic cancer from its histopathological characteristics. It follows that a need exists for methods by which the biological potential, or inherent malignancy, of individual prostatic cancers may be accurately determined.

Park and Lees, in a recent article on the absolute curability of breast cancer, based on current survival statistics, make the following statement, which is, perhaps, applicable to prostatic cancer as well: "From an analysis of the evidence it has been shown that the apparent curability of cancer of the breast can be explained entirely in terms of the variability of growth rate."[30] It is their feeling that, when most observers discuss results of different methods of treatment, they are in reality only measuring differences in the growth rates of biologically different tumors.

TABLE 4. *Recommended plan of treatment for prostatic cancer*

I. Early—i.e. limited to the gland proper, including occult variety
    a. Radical perineal prostatectomy, and
    b. Endocrine therapy
II. Advanced—i.e. beyond the gland proper, with or without metastases
    a. Surgical relief of urinary obstruction, and
    b. Endocrine therapy

Unfortunately, there is no satisfactory method at present for evaluating the growth potential of the individual prostatic cancer. The increased acid phosphatase titer of malignant prostatic tissue, which is reflected in elevated serum levels in most patients with metastatic involvement, is, however, a biological property worthy of further exploration. Nesbit and Baum[31] have analyzed the serum acid and alkaline phosphatase findings in patients with prostatic cancer. They have found that elevation of the serum acid phosphatase level in patients without demonstrable metastases is indicative of a worsened prognosis. Also, they have been able to show that, in patients with metastases, a normal acid phosphatase level is not a sign of low bodily resistance to the disease, and hence does not signify a poor prognosis. The elevation in serum alkaline phosphatase in many patients in response to endocrine treatment is also an interesting and frequent observation, which merits further study.

CONCLUSIONS

At the present time, no satisfactory methods exist for classifying cases of prostatic cancer according to their biological properties. It is apparent, therefore, that we must devote ourselves in increasing measure to basic research in prostatic physiology. Current studies in the intermediary metabolism of phosphorylated compounds, and in certain nutritional aspects of prostatic growth, seem promising. Investigation of growth potentials of heterologously-transplanted human cancers and experimental prostatic tumors, as influenced by hormonal manipulations, may lead to an answer.

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[30] Park, W. W. and Lees, J. C.: Surg., Gynec. & Obst., 93: 129-52, 1951.
[31] Nesbit, R. M. and Baum, W. C.: J. A. M. A., 145: 1321-24, 1951.

The present stalemate which exists in the treatment of prostatic cancer cannot be resolved until we gain a clearer understanding of the nature of the malignant process. Until then, our methods of treatment will of necessity be determined empirically, and we must continue to use the best that combined surgical and endocrine measures can offer (table 4).

SUMMARY

Prostatic cancer presents a formidable challenge today because of its frequency and the difficulty in early diagnosis. The latter factor is largely responsible for the low cure rate in this disease.

Patients with cancer limited to the prostate, including the occult variety, should receive the combined benefit of radical perineal prostatectomy and endocrine therapy, until it can be shown that 10 year survival figures are better in comparable patients treated with endocrine measures alone. The advanced case, whether or not associated with metastases, is best treated by surgical relief of urinary obstruction and hormonal therapy.

The use of radical prostatectomy for borderline cases of advanced prostatic cancer is not recommended.

The validity of current survival statistics for endocrine-treated cases is questioned because of 1) unsatisfactory controls, and 2) the inclusion of patients not dead of prostatic cancer.

The treatment of relapse is discussed briefly.

Emphasis is placed on the necessity of classifying cases according to their biological properties before drawing conclusions as to the effectiveness of different modes of therapy.

The author wishes to express his appreciation to Dr. Robert S. Hotchkiss, Professor and Chairman of the Department of Urology, New York University Post-Graduate Medical School, for his helpful criticism during the preparation of this paper.

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MALIGNANT LYMPHOMA PRIMARILY MANIFESTED AS A TESTICULAR TUMOR

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Testicular tumors are unusual in children. Literature on this subject is principally comprised of individual case reports. Gilbert contributed an exhaustive review of 5,500 testicular tumors, collecting reports from 1803 to 1942. Only 131 cases were found in children. The difficulty in collecting accurate data in regard to testicular tumors is generally recognized. Friedman, Moore and others deserve credit for their efforts to standardize and simplify tumor nomenclature. Prior to this there was much confusion and error. New growths of the male gonad are exceptional to other neoplasms because they do not reproduce testicular tissue while other neoplasms usually reflect the architecture of the tissue in which they originate.

The following case is reported principally to put on record a malignant lymphoma in a child primarily manifested as a testicular tumor. Lymphoma with early involvement of the testes is unusual, but a lymphoma which appears to be primary in the testicle is rare. This case is of further interest because at first it appeared to be an inflammatory process; at the time of exploration, the frozen section suggested a monocellular neoplasm, probably a seminoma. Because of this provisional diagnosis regional lymph node dissection was performed. The true nature of the tumor was not definitely known until later. The concensus of opinion of several pathologists, also that of Col. J. E. Ash and the staff of the Army Institute of Pathology, was that this tumor was a malignant lymphoma, reticulum cell type.

CASE REPORT

No. 93315 J. B., a 4 year old Negro, was admitted to John Gaston Hospital May 23, 1950 with a history of swelling in the right side of the scrotum for approximately one month. He was first seen 2 weeks previous to admission in the outpatient department. The child's mother said that the child had fallen while playing 2 weeks previously and since that time had complained of pain in the right side of the scrotum. The mother believed that no enlargement was present when the child was first seen; however, during the 2 week interval the mass appeared to increase in size and became more painful.

Examination 2 weeks following the supposed injury revealed a small hydrocele which was translucent. The slight degree of enlargement and tenderness in the right side of the scrotum appeared to be confined to the epididymis. A tentative diagnosis of epididymo-orchitis was made and treatment instituted. The child was to return in 1 week for further observation.

During the next examination there appeared to be progressive enlargement of both the testis and epididymis. Permission for exploration of the testicle was granted and the child was immediately admitted to the hospital. There was nothing noteworthy in the past medical history except right cryptorchidism. This was learned from the obstetrical record. The mother was unaware of this condition, and it is assumed that the testicle descended to its normal position in early infancy. A slightly distended abdomen was noted. Several palpable inguinal nodes were detected on the right side. The contents of the right scrotum were approximately twice the size of a normal testis and epididymis. In contradistinction to the previous examination, the mass was no longer translucent nor tender. The urinalysis was negative and a complete blood count was normal. Roentgen examination of the abdomen and chest was entirely negative. Evaluation of Prolan A excretion was not obtained.

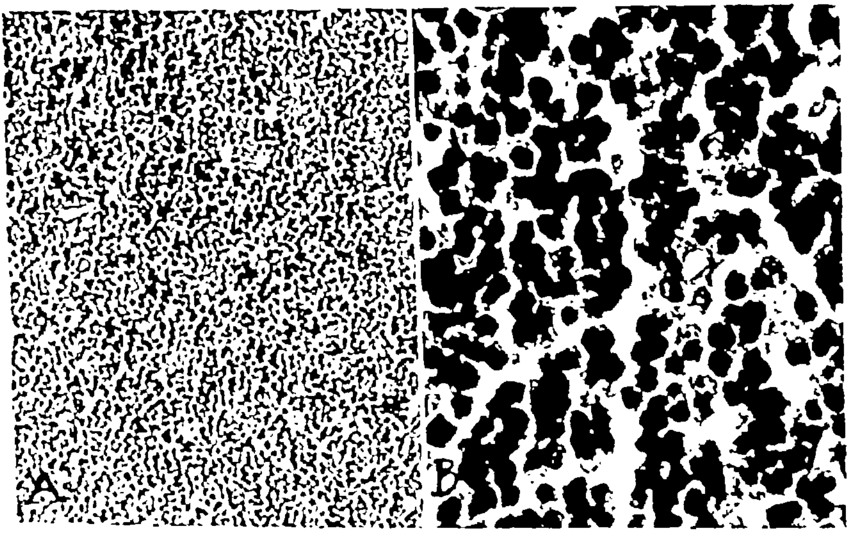

FIG. 1

Exploration was made through a right inguinal incision. The right spermatic cord was isolated and prophylactically clamped with rubber covered forceps before the scrotal contents were inspected. An irregular, whitish-gray tumor with a small amount of clear fluid was found on opening the tunica vaginalis. A frozen section examination of the tumor and a lymph node revealed a malignant neoplasm, probably a seminoma, whereupon the incision was extended and a retroperitoneal block lymph node dissection was done as high as the right renal pedicle. Malignant infiltration was noted in only one lymph node.

The child's immediate recovery was uneventful and he received 1330 r. u. through both anterior and posterior portals after the operative wound had healed.

Pathological report (S 50-1673): An irregular, grayish-white mass which contained two separate nodules was presented. The larger mass measured 5 by 4 by 3 cm. and represented the testis. The epididymis measured 3 by 2 by 1 cm. The testicular capsule appeared to be intact although the testis and epididymis were infiltrated by tumor tissue. Microscopically the tumor was composed of uniform cellular sheets. These cells were mostly polyhedral and had abundant cytoplasm with large amounts of chromatin material (fig. 1). No giant or epithelioid cells were present. The involved lymph node showed the same appearance as the original tumor. A provisional diagnosis of seminoma was made and postoperative radiation was begun as soon as possible. Further study revealed this tumor to be a malignant lymphoma.

Soon after the child returned home low grade fever became evident and a gradual weight loss took place. Approximately 1 month after dismissal from the hospital, a mass appeared in the left upper abdominal quadrant and a roentgenogram of the chest revealed early metastases. The child followed a steady downhill course and expired 3 months later. Unfortunately, the patient could not be studied further after the first postoperative examination and permission for necropsy was refused.

SUMMARY

The mass in the right side of the scrotum of a young colored boy first appeared to be inflammatory.

Two weeks later its malignant nature was more in evidence when it was explored surgically.

The neoplasm involved the right testis and epididymis, and one regional lymph node was found.

Removal of the neoplasm, retroperitoneal block lymph node dissection and postoperative radiation were carried out because of the malignant nature of the tumor although the exact pathological diagnosis was uncertain at that time.

The final pathological diagnosis was: malignant lymphoma, reticulum cell type primarily manifested as a testicular tumor. Unfortunately the child expired several months later, and there was clinical evidence of pulmonary and abdominal metastases. This case represents the misleading innocent appearance of a malignant testicular tumor at the original examination.

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SEMINAL VESICULECTOMY

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The first seminal vesiculectomy was performed in 1889, when Ullman removed tuberculous seminal vesicles through the perineal route.

A few months later, using the inguinal approach, Villeneuve removed, in one block, testicle, vas deferens and seminal vesicle, in a patient having unilateral genital tuberculosis. However, further attempts by other surgeons, did not recommend either of the two techniques.

Roux, Dittel, Schede, Zuckerkandl, Young, Pauchet, among many surgeons, soon modified the perineal technique, the same being done, with the inguinal approach, by Baudet and Duval, Villard and Legueu. Despite this, the progress attained was minimal: several accidents during the operation and bothersome postoperative complications were reported.

These facts called for new surgical techniques. In chronological order, the following routes were used:

a) Trans-ischiatic, with resection of the coccyx (Schede, 1893)

b) Transsacral (after the Kraske technique) with permanent bone resection (Schede, 1894; Routier, 1898)

c) Suprapubic (Young, 1900)

d) Trans-ischiatic, with temporary resection of the coccyx, according to the Levy-Schlange technique (Cholzoff, 1905)

e) Ischiorectal (Voelcker, 1908)

f) Inguinoperineal (Marion, 1909; Pauchet, 1909)

g) Coccyperineal (Fiolle, 1911)

h) Transrectal (Saposhkoff, 1922)

i) Transvesical (Thomson Walker, 1924)

j) Transperitoneal (Seymour, 1932)

Thus far, however, seminal vesiculectomy has not entered the surgical routine and has been the privilege of a few urological services in the United States and Germany.

The situation of the vesicles, deeply guarded in the lesser pelvis, does not offer adequate field to such delicate maneuvers, unless there is wide exposure. This fact, as expected, focussed the attention of the surgeons at all times, and all the routes that could lead one to the lesser pelvis were searched. That is the reason all the aforementioned approaches were tried.

Nowadays, for many reasons, two routes are mostly used: the perineal, mainly in the U. S.; and the transischiorectal in Germany.

I have always had difficulties and performed incompleted operations complicated by many accidents, when using the ischiorectal approach to the seminal vesicles. In Europe, I have seen the same mishap in the hands of very experienced surgeons.

Doubtless, the ischiorectal route gives better exposure and, consequently, better visibility and control than the perineal one.

I have never been very fond of the perineal approach. It is well known by all of us how deep and narrow the field is when yielded by this route; wedge-shaped on its upper extremity, a good visual control of the maneuvers is not always possible and the operation is mostly done by blind finger dissection, chiefly in the more delicate and difficult steps.

This opinion is not an isolated one. Fuller tried to remove the seminal vesicles through the perineum. Adhesions and friability, narrow field, lack of visual control, created unfavorable conditions for the performance of the operation, which could not be done as previously planned. The only thing that could be done was a single drainage, seminal vesiculotomy. From then on, he abandoned the practice of the seminal vesiculectomy and performed perineal vesiculotomy in 700 cases, for treatment of nonspecific inflammatory processes, with satisfactory results. But the operation was a complete failure in 7 cases of tuberculous spermatocystitis.

Squier modified Fuller's technique, thereby obtaining good exposure of the seminal vesicles for drainage under visual control.

Cunningham used Squier's technique in 116 seminal vesiculotomies, without casualties. He states that in some cases the adherence between the vesicles and their fascia is so marked that it is impossible to free them; in this instance, the seminal vesicles should be opened without being freed from their thick fibromuscular envelopes.

Morrissey and Smith were not convinced about the advantages of the technical improvements introduced by Squier, Young and Cunningham in the perineal approach, and made new modifications, so as to improve the exposure and lessen the operative accidents and risks. They performed this perineal operation 135 times, among seminal vesiculotomies (more often) and seminal vesiculectomies. They stress the operative difficulties and present two pictures, from which one can see how small the specimen removed was.

Young, notwithstanding his mastered experience with the perineal approaches, points out extreme difficulties, mainly in the liberation of the vas and base of the vesicles, when dense adhesions have developed as a consequence of the inflammatory process.

Gutierrez is very enthusiastic about perineal seminal vesiculectomy. He performed it 100 times, most of them during the years of 1923 and 1924, reporting no accidents or deaths. His patients were insane subjects admitted to the New Jersey Neuropsychiatric Hospital and the operations were done to eliminate probable infectious foci. In several of his cases, according to his statistics, there was no inflammation of the seminal vesicles and, in a great many cases, there was a slight nonspecific inflammation. However, Gutierrez also calls our attention to the technical difficulties in the freeing of the seminal vesicles, when there is perivesiculitis.

From what has been said in the preceding paragraphs, we can see that there is an agreement among the surgeons about the technical difficulties of the perineal approach, especially in the cases where the operation is indicated, i.e., the chronic inflammatory processes, specific or nonspecific, with perivesicular inflammatory reaction. To this fact we can add the possibility of bladder, rectal or peritoneal injuries, besides the great trauma to the bladder and prostate caused by hard pulling.

These circumstances directed me to approach the seminal vesicles through the suprapubic route, by which means the widest exposure for operations in the lesser pelvis is obtained. This operation has nothing in common with the Young's technique, described in 1900, and soon abandoned. As a matter of fact, they are different, step by step including the abdominal wall incision.

OPERATIVE TECHNIQUE

A suprapubic midline incision is made starting at the level of the symphysis and ending 2 or 3 cm. below the umbilicus. After the skin, subcutaneous tissue and rectus fascia are opened, the recti muscles are separated, and the prevesical and preperitoneal fatty connective tissue, covered by the transversalis fascia, is entered. Using a sponge-stick or a compress, the fatty connective tissue that covers the peritoneal cul-de-sac is pushed upwards. The structures being well recognized, two Allis forceps are placed, one in the bladder and the other above in the median umbilicovesical ligament. By pulling the two forceps in opposite directions, the exact place where the peritoneum reflects in the bladder is found. At this site, the peritoneum is opened by a transverse incision, about 3 or 4 cm. long, the patient having been previously placed in Trendelenburg position. Once the peritoneal cavity is opened, the zone of adherence between the peritoneum and bladder is determined. The serous membrane is incised again, immediately below this zone of adherence and over the bladder, care being taken not to cut on the vesical wall. This second incision is slightly larger than the first one, and the two incisions meet at the level of their angles. The peritoneum is freed from the pelvic connective tissue, leaving the bladder (and the incised peritoneum, which covers the bladder wall) forward and outward. The peritoneal cavity is then closed by a running stitch with catgut. The liberation of the space of Douglas is completed so that the rectovesical space is exposed: the anterior surface of the rectum is posterior, the bladder base is anterior and in between lie the prostate, seminal vesicles and the terminal portions of the vasa.

At this moment, the ureters are seen, bulging through their cellular coverings, running obliquely on each side of the midline, downwards, forwards, and inwards. The iliac vessels are observed and crossing them anteriorly on each side, the vas is recognized and taken on a Babcock forceps. A piece of gauze is passed underneath the vas on each side before they are doubly ligated with No 2 chromic catgut, cut and coagulated. Each inner stump (pelvic stump) of the vas is then held by a sponge forceps and the canal freed as it runs through the lesser pelvis. This step is not difficult, since the vas is only covered by the fascia abdominalis propria. A self-retaining retractor (we use De Quervain's) is substituted and a pliable retractor is placed in the upper angle of the wound, to retract the peritoneal cul-de-sac, thereby a good exposure of the pelvirectal space being obtained.

Then, the surgeon takes, with his left hand, the two sponge forceps previously placed in the vas stumps and, with scissors dissection, the two deferens are freed until they penetrate the thick fibromuscular envelopes of the seminal vesicles. When the upper, external ends of this covering are reached, the surgical vascular pedicle of the gland is identified, doubly ligated and cut. At this site the vesiculo-deferential artery enters the fibrous muscular covering of the vesicle.

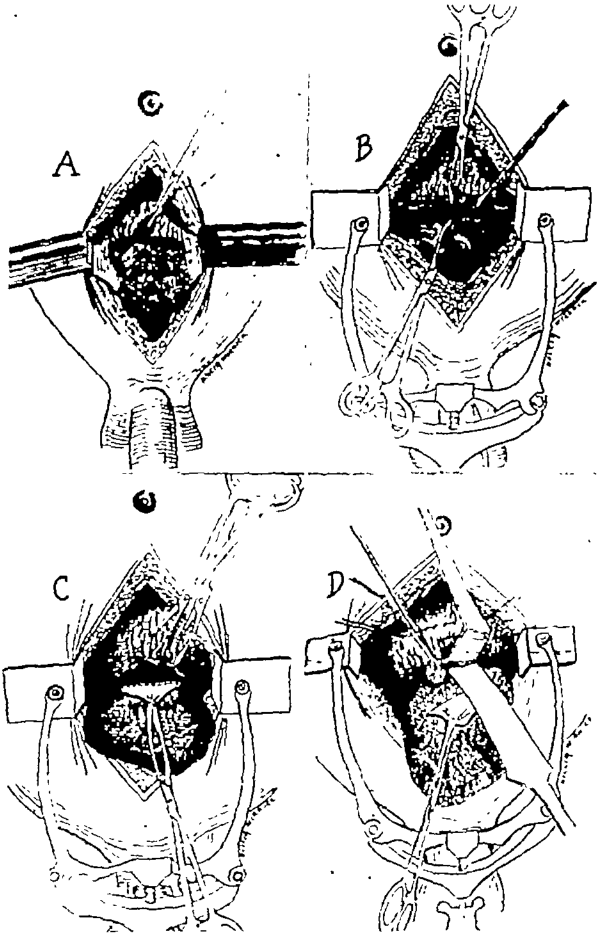

FIG. 1. *A*, freeing connective tissue that covers bladder and hides peritoneal cul-de-sac. *B*, two Allis clamps have been placed in peritoneum and bladder; traction is applied in opposite directions so as to detect exact line of adherence between two structures. At this site, peritoneum is opened. *C*, parietal peritoneum has been opened. Dotted line shows second peritoneal incision, made just below line of adhesion between bladder and serous membrane. *D*, peritoneal incision has been closed; bladder is now extraperitoneal. Using a sponge stick, bladder is being freed from cul-de-sac of Douglas. Rectum is seen posteriorly; prostate and seminal vesicles, anteriorly.

The next step is essential; instead of opening the thick posterior layer of the vesicular bed, which covers and hides the gland, the surgeon places there one or two Allis forceps for traction. The surgeon's left hand takes the forceps that hold the two vasa and the ones placed in the seminal vesicle capsule; when the time comes, these forceps will be used to pull backwards the seminal vesicles and its capsule. A Deaver retractor is placed deeply in the bladder base. The

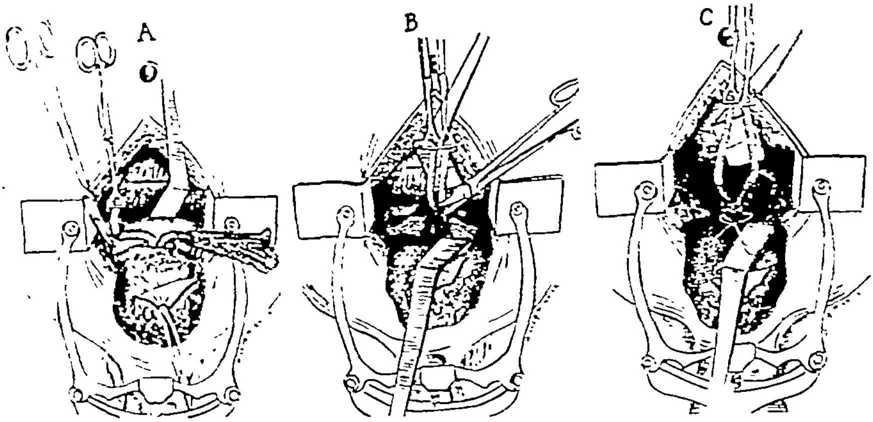

FIG. 2. *A*, vasa deferentia exposed after crossing external iliac vessels; loop of gauze is passed under them. Then, they are cut across, between two ligatures (with chromic catgut No. 1); pelvic stump is held with traction forceps, so as to make dissection down to seminal vesicles' capsule easier. *B*, by following vasa, seminal vesicles' capsule is being free. Note that dissection is carried out with curved scissors, tip being directed towards vesicles' capsule in order to avoid injuries to bladder or ureters. Dissection is begun anteriorly, then carried out laterally until prostate base, where ejaculatory ducti penetrate, is reached. *C*, dissection completed. Ejaculatory ducts are ligated with No. 1 chromic catgut. Specimen is removed, ejaculatory ducts being cut with electric knife.

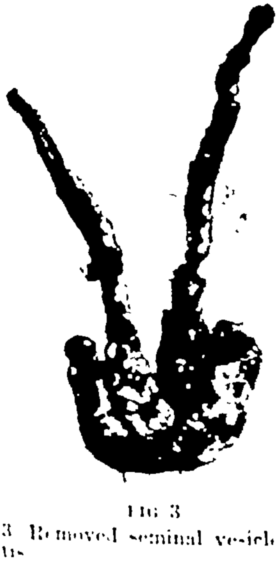

FIG. 3

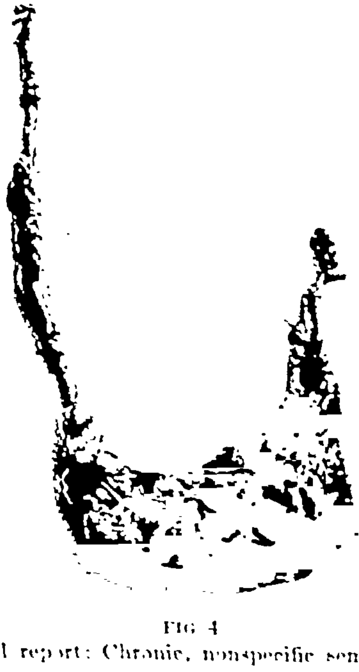

FIG. 4

FIG. 3. Removed seminal vesicles. Pathological report: Chronic, nonspecific seminal vesiculitis.

FIG. 4. Photograph of tuberculous seminal vesicles; capsule is still in place. Pathological report: Chronic tuberculous seminal vesiculitis.

left hand is then gently directed backwards and the cleavage between bladder and seminal vesicles is exposed.

Under visual control, the liberation of the two organs is started, using long

Doubtless, the ischiorectal route gives better exposure and, consequently, better visibility and control than the perineal one.

I have never been very fond of the perineal approach. It is well known by all of us how deep and narrow the field is when yielded by this route; wedge-shaped on its upper extremity, a good visual control of the maneuvers is not always possible and the operation is mostly done by blind finger dissection, chiefly in the more delicate and difficult steps.

This opinion is not an isolated one. Fuller tried to remove the seminal vesicles through the perineum. Adhesions and friability, narrow field, lack of visual control, created unfavorable conditions for the performance of the operation, which could not be done as previously planned. The only thing that could be done was a single drainage, seminal vesiculotomy. From then on, he abandoned the practice of the seminal vesiculectomy and performed perineal vesiculotomy in 700 cases, for treatment of nonspecific inflammatory processes, with satisfactory results. But the operation was a complete failure in 7 cases of tuberculous spermatocystitis.

Squier modified Fuller's technique, thereby obtaining good exposure of the seminal vesicles for drainage under visual control.

Cunningham used Squier's technique in 116 seminal vesiculotomies, without casualties. He states that in some cases the adherence between the vesicles and their fascia is so marked that it is impossible to free them; in this instance, the seminal vesicles should be opened without being freed from their thick fibromuscular envelopes.

Morrissey and Smith were not convinced about the advantages of the technical improvements introduced by Squier, Young and Cunningham in the perineal approach, and made new modifications, so as to improve the exposure and lessen the operative accidents and risks. They performed this perineal operation 135 times, among seminal vesiculotomies (more often) and seminal vesiculectomies. They stress the operative difficulties and present two pictures, from which one can see how small the specimen removed was.

Young, notwithstanding his mastered experience with the perineal approaches, points out extreme difficulties, mainly in the liberation of the vas and base of the vesicles, when dense adhesions have developed as a consequence of the inflammatory process.

Gutierrez is very enthusiastic about perineal seminal vesiculectomy. He performed it 100 times, most of them during the years of 1923 and 1924, reporting no accidents or deaths. His patients were insane subjects admitted to the New Jersey Neuropsychiatric Hospital and the operations were done to eliminate probable infectious foci. In several of his cases, according to his statistics, there was no inflammation of the seminal vesicles and, in a great many cases, there was a slight nonspecific inflammation. However, Gutierrez also calls our attention to the technical difficulties in the freeing of the seminal vesicles, when there is perivesiculitis.

From what has been said in the preceding paragraphs, we can see that there is an agreement among the surgeons about the technical difficulties of the perineal approach, especially in the cases where the operation is indicated, i.e.,

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SEMINAL VESICULECTOMY

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The first seminal vesiculectomy was performed in 1889, when Ullman removed tuberculous seminal vesicles through the perineal route.

A few months later, using the inguinal approach, Villeneuve removed, in one block, testicle, vas deferens and seminal vesicle, in a patient having unilateral genital tuberculosis. However, further attempts by other surgeons, did not recommend either of the two techniques.

Roux, Dittel, Schede, Zuckerkandl, Young, Pauchet, among many surgeons, soon modified the perineal technique, the same being done, with the inguinal approach, by Baudet and Duval, Villard and Legueu. Despite this, the progress attained was minimal; several accidents during the operation and bothersome postoperative complications were reported.

These facts called for new surgical techniques. In chronological order, the following routes were used:

a) Trans-ischiatic, with resection of the coccyx (Schede, 1893)

b) Transsacral (after the Kraske technique) with permanent bone resection (Schede, 1894; Routier, 1898)

c) Suprapubic (Young, 1900)

d) Trans-ischiatic, with temporary resection of the coccyx, according to the Levy-Schlange technique (Cholzoff, 1905)

e) Ischiorectal (Voelcker, 1908)

f) Inguinoperineal (Marion, 1909; Pauchet, 1909)

g) Coccyperineal (Fiolle, 1911)

h) Transrectal (Saposhkoff, 1922)

i) Transvesical (Thomson Walker, 1924)

j) Transperitoneal (Seymour, 1932)

Thus far, however, seminal vesiculectomy has not entered the surgical routine and has been the privilege of a few urological services in the United States and Germany.

The situation of the vesicles, deeply guarded in the lesser pelvis, does not offer adequate field to such delicate maneuvers, unless there is wide exposure. This fact, as expected, focussed the attention of the surgeons at all times, and all the routes that could lead one to the lesser pelvis were searched. That is the reason all the aforementioned approaches were tried.

Nowadays, for many reasons, two routes are mostly used: the perineal, mainly in the U. S.; and the transischiorectal in Germany.

I have always had difficulties and performed incompleted operations complicated by many accidents, when using the ischiorectal approach to the seminal vesicles. In Europe, I have seen the same mishap in the hands of very experienced surgeons.

placed in the vas stumps and, with scissors dissection, the two deferens are freed until they penetrate the thick fibromuscular envelopes of the seminal vesicles. When the upper, external ends of this covering are reached, the surgical vascular pedicle of the gland is identified, doubly ligated and cut. At this site the vesiculo-deferential artery enters the fibrous muscular covering of the vesicle.

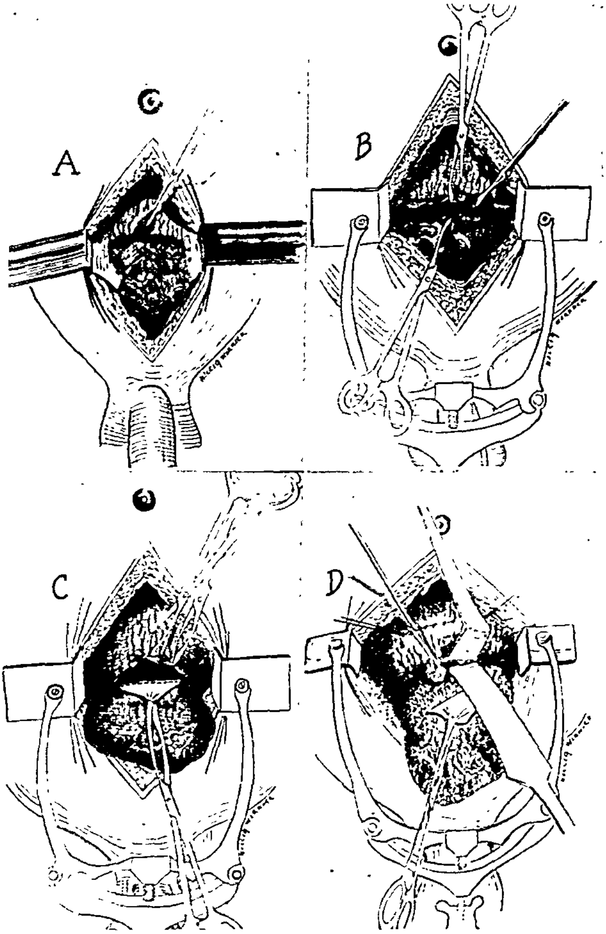

FIG. 1. *A*, freeing connective tissue that covers bladder and hides peritoneal cul-de-sac. *B*, two Allis clamps have been placed in peritoneum and bladder; traction is applied in opposite directions so as to detect exact line of adherence between two structures. At this site, peritoneum is opened. *C*, parietal peritoneum has been opened. Dotted line shows second peritoneal incision, made just below line of adhesion between bladder and serous membrane. *D*, peritoneal incision has been closed; bladder is now extraperitoneal. Using a sponge stick, bladder is being freed from cul-de-sac of Douglas. Rectum is seen posteriorly; prostate and seminal vesicles, anteriorly.

The next step is essential; instead of opening the thick posterior layer of the vesicular bed, which covers and hides the gland, the surgeon places there one or two Allis forceps for traction. The surgeon's left hand takes the forceps that hold the two vasa and the ones placed in the seminal vesicle capsule; when the time comes, these forceps will be used to pull backwards the seminal vesicles and its capsule. A Deaver retractor is placed deeply in the bladder base. The

the chronic inflammatory processes, specific or nonspecific, with perivesicular inflammatory reaction. To this fact we can add the possibility of bladder, rectal or peritoneal injuries, besides the great trauma to the bladder and prostate caused by hard pulling.

These circumstances directed me to approach the seminal vesicles through the suprapubic route, by which means the widest exposure for operations in the lesser pelvis is obtained. This operation has nothing in common with the Young's technique, described in 1900, and soon abandoned. As a matter of fact, they are different, step by step including the abdominal wall incision.

OPERATIVE TECHNIQUE

A suprapubic midline incision is made starting at the level of the symphysis and ending 2 or 3 cm. below the umbilicus. After the skin, subcutaneous tissue and rectus fascia are opened, the recti muscles are separated, and the prevesical and preperitoneal fatty connective tissue, covered by the transversalis fascia, is entered. Using a sponge-stick or a compress, the fatty connective tissue that covers the peritoneal cul-de-sac is pushed upwards. The structures being well recognized, two Allis forceps are placed, one in the bladder and the other above in the median umbilicovesical ligament. By pulling the two forceps in opposite directions, the exact place where the peritoneum reflects in the bladder is found. At this site, the peritoneum is opened by a transverse incision, about 3 or 4 cm. long, the patient having been previously placed in Trendelenburg position. Once the peritoneal cavity is opened, the zone of adherence between the peritoneum and bladder is determined. The serous membrane is incised again, immediately below this zone of adherence and over the bladder, care being taken not to cut on the vesical wall. This second incision is slightly larger than the first one, and the two incisions meet at the level of their angles. The peritoneum is freed from the pelvic connective tissue, leaving the bladder (and the incised peritoneum, which covers the bladder wall) forward and outward. The peritoneal cavity is then closed by a running stitch with catgut. The liberation of the space of Douglas is completed so that the rectovesical space is exposed; the anterior surface of the rectum is posterior, the bladder base is anterior and in between lie the prostate, seminal vesicles and the terminal portions of the vasa.

At this moment, the ureters are seen, bulging through their cellular coverings, running obliquely on each side of the midline, downwards, forwards, and inwards. The iliac vessels are observed and crossing them anteriorly on each side, the vas is recognized and taken on a Babcock forceps. A piece of gauze is passed underneath the vas on each side before they are doubly ligated with No. 2 chromic catgut, cut and coagulated. Each inner stump (pelvic stump) of the vas is then held by a sponge forceps and the canal freed as it runs through the lesser pelvis. This step is not difficult, since the vas is only covered by the fascia abdominalis propria. A self-retaining retractor (we use De Quervain's) is substituted and a pliable retractor is placed in the upper angle of the wound, to retract the peritoneal cul-de-sac, thereby a good exposure of the pelvirectal space is obtained.

Then, the surgeon takes, with his left hand, the two sponge forceps previously and curved scissors, cutting towards the seminal vesicle capsule, so as to avoid any injury to the bladder or even to the ureters. Experience has shown that even in cases of perivesiculitis, more marked in old tuberculous spermatocystitis, it is always possible to find the cleavage. Good lights are necessary, so as to make it possible for the surgeon to see his dissection. Carrying the dissection forwards, and laterally, the base of the prostate is exposed and the site

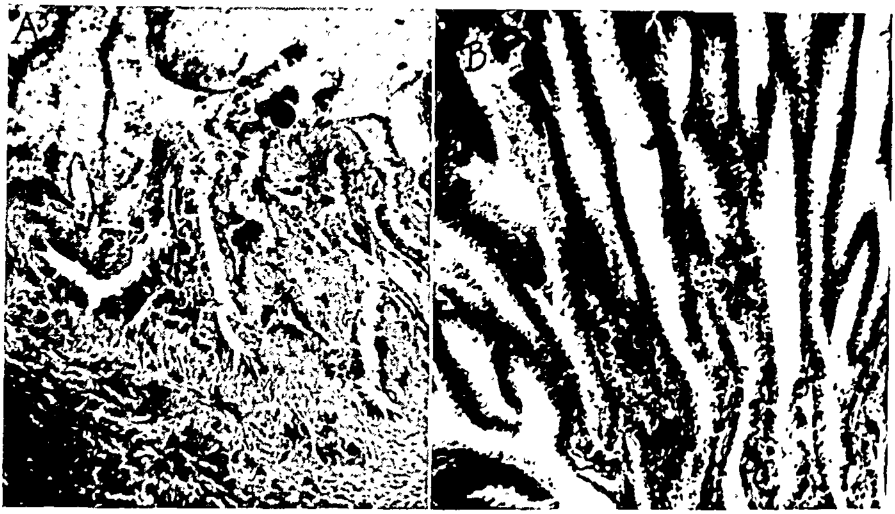

FIG. 5. *A*, chronic seminal vesiculitis, with atrophic changes. Hypertrophy of papillary-like septa and catarrh of mucous membrane. In lumen, adherent to crypt, there are corpora amylacea. *B*, chronic nonspecific seminal vesiculitis. Round cell infiltration, more or less marked, of vascular-connective stalk of septa.

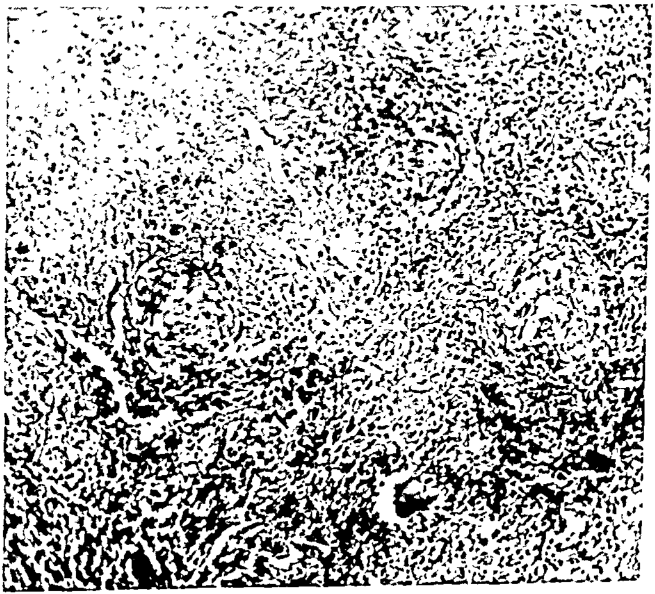

FIG. 6. Tuberculosis of seminal vesicles. On right, lower third, multinuclear giant cell; above, two tubercles. On left upper corner, caseous degeneration.

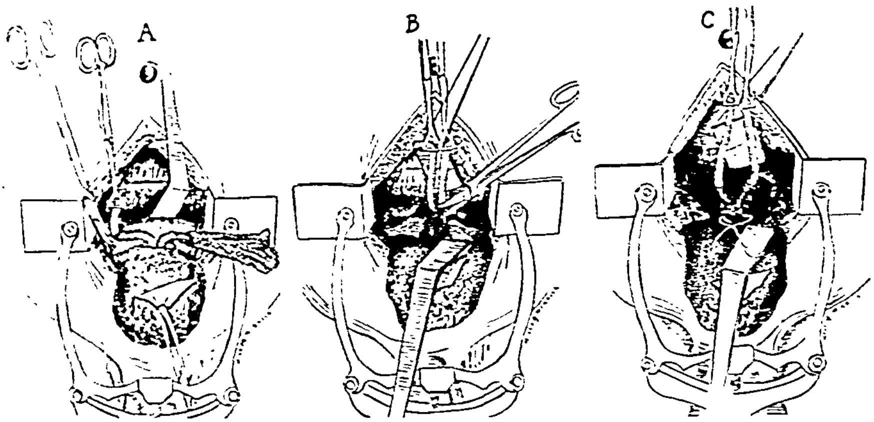

FIG. 2. *A*, vasa deferentia exposed after crossing external iliac vessels; loop of gauze is passed under them. Then, they are cut across, between two ligatures (with chromic catgut No. 1); pelvic stump is held with traction forceps, so as to make dissection down to seminal vesicles' capsule easier. *B*, by following vasa, seminal vesicles' capsule is being free. Note that dissection is carried out with curved scissors, tip being directed towards vesicles' capsule in order to avoid injuries to bladder or ureters. Dissection is begun anteriorly, then carried out laterally until prostate base, where ejaculatory ducti penetrate, is reached. *C*, dissection completed. Ejaculatory ducts are ligated with No. 1 chromic catgut. Specimen is removed, ejaculatory ducts being cut with electric knife.

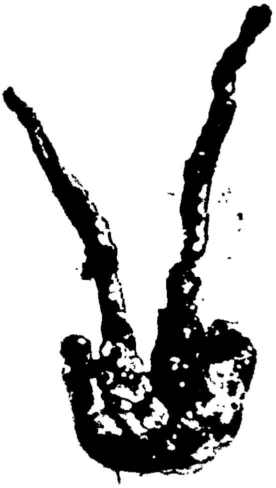

FIG 3

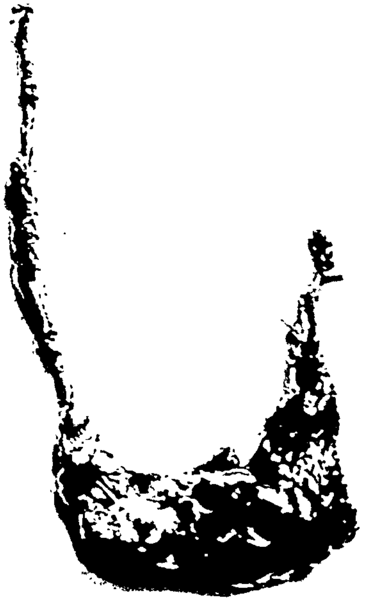

FIG 4

FIG. 3 Removed seminal vesicles. Pathological report: Chronic, nonspecific seminal vesiculitis.

FIG. 4 Photograph of tuberculous seminal vesicles; capsule is still in place. Pathological report Chronic tuberculous seminal vesiculitis.

Left hand is then gently directed backwards and the cleavage between bladder and seminal vesicles is exposed.

Under visual control, the liberation of the two organs is started, using long

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FAILURE OF FUSION OF THE TESTIS AND EPIDIDYMIS

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The purpose of this paper is to report a case of bilateral undescended testis with bilateral complete separation of the testis and epididymis. A search of the literature failed to find any record of a similar case, although 20 cases of unilateral separation of testis and epididymis have been reported. Three additional cases of the latter anomaly have been found in the files of the University Service of the Grace-New Haven Hospital.

Separation of the testis and epididymis was recorded as early as 1851.[1] The condition has been observed much more frequently in undescended testis than when the testes have been normally situated in the scrotum.[2, 3, 4, 5]

Hobday[6] mentioned that in horses the testis and epididymis frequently may be separated, with the testis usually in the abdomen, and the epididymis in the inguinal canal. If castration is attempted in such cases, only the epididymis is commonly removed, and with continued internal secretions from the testis the animal may continue to show the usual male characteristics.

Windholz[5] reported a case of separation of the testis and epididymis in incomplete descent of the testis, and classified four types of abnormal testis-epididymis relationship:

1) Congenital anorchism with descent of the vas and epididymis.

2) Undescended testis, with descent of the epididymis and vas, and separation of the testis and epididymis.

3) Vas deferens alone present in the scrotum with testis and epididymis undescended.

4) Partial separation of the testis and epididymis (dislocation) more often seen when both are undescended.

More recently separation of testis and epididymis has been reported in the American literature.[7, 8] Lazarus and Marks[9] in an excellent review of the problem, noted that it is probably the most rare anomaly associated with the undescended testis. Our study also indicates that this anomaly is one of the most unusual abnormalities affecting the undescended testis.

In all recorded instances of separation of the testis and epididymis, the epididymis has been situated lower in the inguinal canal than the testis. We believe this fact should be emphasized because at operation, if the structures are not accurately identified, it is likely that only the epididymis will be placed in the scrotum, and the unrecognized testis will remain in its intra-abdominal position.

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[3] Budinger: Arch. f. klin. Chir., **95:** 140–160, 1911.

[4] Kaufman: Lehrbuch der Speziellen Pathologischen Anatomie. Berlin, 1909, vol. 2, p. 881.

[5] Windholz, F.: Klin. Wochnschr., **47:** 2175, 1923.

[6] Hobday, F. T. G.: Proc. Royal Soc. Med., Sect. Comparative Medicine, **17:** 3–17, 1924.

[7] Wangensteen, O. H.: Arch. Surg., **14:** 663–732, 1927.

[8] Wangensteen, O. H.: Surg., Gynec. & Obst., **54:** 219, 1932.

[9] Lazaras, J. A. and Marks, M. S.: J. Urol., **57:** 567–574, 1947.

where the extremities of the vesicles penetrate the prostate is identified. The ejaculatory ducts are recognized, doubly ligated and cut, thereby removing in one piece the encapsulated seminal vesicles, the vasa deferentia and their ampules. The small rent left in the prostate capsule is closed with two or three stitches of No. 0 catgut, using the boomerang needle, at the same time burying the stumps of the ejaculatory ducts.

This way an extracapsular seminal vesiculectomy is performed. The specimen is encapsulated, therefore there is less danger of rupturing the weak walls of the seminal vesicles.

After completing the hemostasis, the operative wound is revised and abdominal wall closed by layers. A Penrose drain is left in the retrovesical space (except in the case of tuberculous infection) and an indwelling urethral catheter left for 24 hours. In this operation, we remove in one piece, seminal vesicles, the ampulla, and also the pelvic portion (if it is desirable, the iliac portion too) of the vasa deferentia. Therefore, there is a complete removal of the spermatic pathways. The convalescence is always calm, the patient being up and about on the fourth to sixth day.

See figures 1, 2, 3, 4, 5, 6.

SUMMARY

The author presents a description of a new technique for the removal of the seminal vesicles and internal spermatic pathways.

There is wide exposure, making possible the visual control of all the operative maneuvers, and the extracapsular removal of the seminal vesicles, abolishing the annoying possibility of rupture of the organ, in cases of tuberculosis or malignancy.

The operation performs a bilateral, suprapubic, subperitoneal, retrovesical and extracapsular seminal vesiculectomy.

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testis" from the surrounding areolar tissue, there suddenly emerged from the internal ring a second rounded, well encapsulated structure, likewise measuring 1.5 to 2.0 cm. in diameter. This latter object was connected with the former only by a small artery and vein 5.0 cm. in length.

Frozen section biopsy of the two organs showed that the structure situated low in the inguinal canal was epididymis, while the structure which had been located retroperitoneally was an atrophic testis. After teasing free the blood supply of the testis, it was fixed in the scrotum by a cotton suture passed through its lower pole and brought out through the scrotum. This suture later was attached to the thigh with adhesive plaster. The epididymis was also fixed in the scrotum and a purse-string suture was placed at the junction of the scrotum and inguinal canal. The hernia was repaired by a modified Ferguson operation.

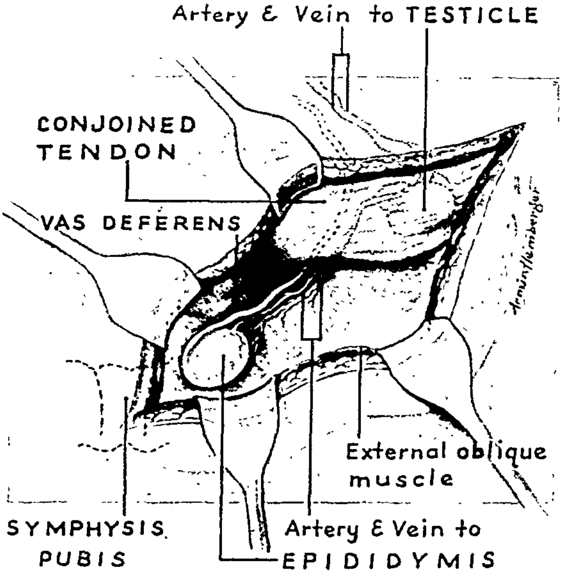

FIG. 1

The postoperative course was uncomplicated, and in 7 days the cotton traction suture was removed. The testis and epididymis remained high in the scrotum.

In August 1950, the right inguinal canal was explored and the same anomaly was found. The epididymis was at the lower end of the inguinal canal, and the testicle was situated in the retroperitoneal area within the internal inguinal ring. The vas was attached to the lower lying epididymis, and the testis and epididymis were connected only by an artery and vein of small calibre.

Figure 1 illustrates the operative findings, which were identical on both sides.

Examination of the records of the Grace-New Haven Hospital showed that between 1926 and 1950, 245 patients had been operated upon either for undescended testes, or had been noted to have undescended testes at the autopsy table. In 3 of these patients, all of whom were operative cases, separation of the testis

Table 1 recapitulates the reported cases of separation of the testis and epididymis.

CASE REPORTS

A. P., aged 12, was admitted to the Windham Community Memorial Hospital in November 1949, for surgical correction of his undescended testes. Since the patient's birth, absence of scrotal testes had been noted. Intermittently, however, a round mass about 2 cm. in diameter had been found in the left inguinal canal, or high in the left side of the scrotum. Growth and secondary sexual characteristics had developed normally.

TABLE 1

YEAR	AUTHOR	REMARKS
1851	Follin[1]	1 case
1861	Godard[2]	1 case
1911	Budinger[3]	"occurs frequently"
1922	Kaufman[4]	1 case
1923	Windholz[5]	1 case
1923	Ombrédanne[10]	"occasionally occurs"
1924	Hobday[6]	"occasionally in horses"
1927	Wangensteen[7]	"occasionally found"
1929	Brunzema[11]	4 cases
1932	Wangensteen[8]	6 cases mentioned
1939	Wilson[12]	1 case
1942	Blanke and Doerr[13]	1 case
1946	Badenoch[14]	3 cases
1947	Lazarus and Marks[9]	1 case
	Total	20—all unilateral

The patient was well nourished and well developed. Vital signs were normal. Pertinent findings were limited to the genitalia. Pubic hair distribution was normal. The penis was circumcised and of normal size. The scrotum was atrophic and neither testis was palpable in it. No masses were present in the right inguinal canal. At the left external inguinal ring, a round, smooth mass, two centimeters in diameter, was palpable. It could be drawn downward as far as the upper portion of the scrotum. Both external rings were relaxed, and an indirect hernia was present on each side.

The decision was made to perform orchiopexy and inguinal hernia repair on the two sides at separate operations. Accordingly, on November 26, 1949, left orchiopexy and herniorrhaphy was performed. At the lower end of the inguinal canal there was found a solid structure which at first was thought to be testis. It was round, well encapsulated, measured about 1.5 cm. in diameter, and was attached to the vas deferens. While attempting to free the vascular supply of this "atrophic of fusion has not been described in normally descended testes. In all recorded instances of separation of the testis and epididymis, the testis always has been undescended, located cephalad to the epididymis. This suggests that fusion with the epididymis is essential to normal descent of the testis. No instances were found in which a testis descended into the scrotum without its accompanying epididymis, although the reverse is true.

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When no connection exists for the passage of sperm from the testis to the vas bilaterally, as in the first case presented, sterility is a problem for therapy. The future may offer some hope to these prepubertal patients if anastomosis between the testis and vas, or testis and epididymis should prove feasible.

SUMMARY

An instance of bilateral failure of fusion of the testis and epididymis is reported in detail. Three unilateral cases of failure of fusion are added also to the 20 such cases reported in the literature. The importance of thorough examination of the spermatic cord and its contents at operation is emphasized, because if the testis and epididymis are separated and each is not clearly identified, the epididymis alone may be placed in the scrotum while the testis remains in its abnormal position.

The authors wish to thank Dr. Clyde L. Deming for the privilege of examining his case records in the preparation of the manuscript.

and epididymis was discovered on one side. Tables 2 and 3 represent the statistical findings.

Complete separation of the testis and epididymis occurred in 1.2 per cent of all cases of undescended testes anatomically examined.

1) Patient No. C10788 was an 8-year old boy who had had an undescended left testis since birth. At intervals it would descend into the scrotum temporarily. At operation the vas deferens was found to extend into the scrotum ending in a few epididymal tubules, and a small testis was indentified in the midportion of the inguinal canal. No connection could be demonstrated between the vas and the remnant of the epididymis and the testis.

2) Patient No. 88474 was a man of 20 years, whose right testis had been undescended since birth. For the year preceding his hospital admission, pain in the right inguinal canal had been a prominent complaint. Surgical exploration showed the epididymis situated in the middle third of the inguinal canal within a closed sac of peritoneum. The testis was found in the abdomen some distance proximal to the epididymis.

TABLE 2. *Undescended Testis in the Grace-New Haven Hospital*

1926–1950

	Cases
Total cases seen clinically	309
Total cases anatomically examined	245
Bilateral undescended testis	81
Right undescended testis	73
Left undescended testis	83
Not mentioned as to laterality	8

TABLE 3. *Anomalies associated with undescended testis*

	Cases
Elongated epididymis	7
Anorchia	11
Absent epididymis	3
Complete separation of testis and epididymis	3

3) Patient No. 85680 was a 19-year old Negro who had had a testis fixed near the right pubic bone since birth. The left testis had been undescended until puberty, when it moved into the scrotum. At operation the right epididymis was thin and elongated. It was located 1.5 cm. from the testis, and was connected with it only by an insignificant fibrous band.

DISCUSSION

It appears reasonable to assume that separation of the testis and epididymis should occur on occasion, because they develop from separate anlage, and their subsequent natural history is somewhat complicated. The testis arises as a localized outgrowth of the medial portion of the urogenital ridge. The epididymis originates from a collection of the proximal tubules of the mesonephric duct and the duct itself. For a perfect anatomical result, there must be not only fusion of the two organs, but also descent of the two into the scrotum. Complete failure connective tissue. The seminiferous tubules were quite cellular and were not involved in any neoplastic or inflammatory process. The tumor was reported as an ectopic spleen attached to the upper pole of the left testis.

Case 2. E. R. S., a 69 year old white man, fell from a tree and was dead on arrival at the Portland General Hospital. A coroner's autopsy was ordered since the patient had been well prior to his fall. Cause of death was determined to be due to a rupture of the thoracic aorta with resulting hemorrhage into the mediastinum. The following gross specimen to be described was found as an incidental feature of this autopsy.

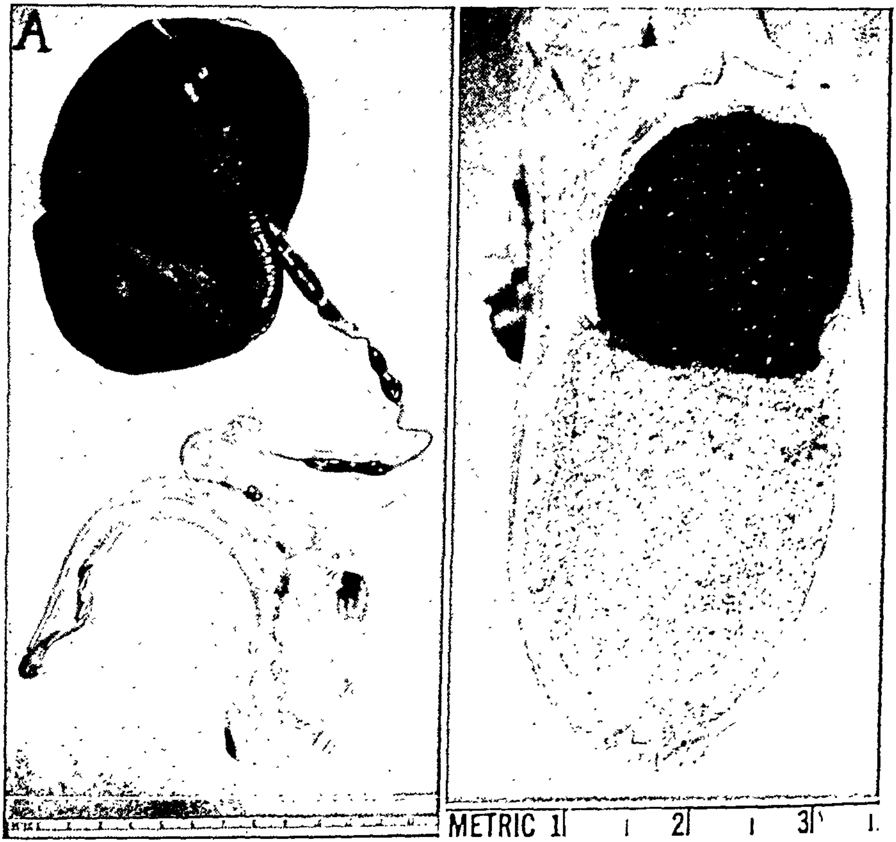

FIG. 1. *A*, autopsy specimen with parent spleen and accessory spleens extending into left scrotum. *B*, cross section of accessory scrotal spleen and testis.

With the abdominal cavity open, the various organs were noted to occupy their usual relationships. On mobilizing the spleen in the left upper quadrant, it was found to have a sharp anterior margin with the usual notches present (fig. 1, *A*). A single cleft on the lateral surface, divided the structure into two lobes of approximate equal size. A finger-like process of splenic tissue extended downward from the lower pole of the spleen and was continuous with an intra-abdominal fibrous cord containing multiple small nodules of dark red tissue. These

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ACCESSORY SPLEEN IN SCROTUM: REPORT OF TWO CASES

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The surgical removal of an accessory spleen from the left scrotal compartment first focused our attention on this comparatively rare anomaly. A second case, with multiple ectopic spleens extending into the left scrotum, was recently discovered at autopsy. The possible clinical significance and paucity of reported cases seems to justify at least a short description of these two cases.

Eleven recorded instances of this anomaly are to be found in the foreign and domestic literature. The first case reported by Sneath[1] in 1913 exhibited the characteristic features as later described in cases reported by Heitzmann, Skworozoff,[2] and by Talman.[3] Sneath described a 2 by 1 cm. mass of splenic tissue attached to the upper pole of the left testis. An attached cord-like structure extended up through the left inguinal canal where it passed behind the peritoneum to its termination at the lower pole of the spleen. Similar cases exhibiting this cord-like structure have been reported by Olken,[4] by Andrews and Etters,[5] and more recently by Tate and Goforth.[6]

CASE REPORTS

J. L. C., a 4 year old white boy, was admitted to Doernbecher Childrens Hospital for the surgical correction of a congenital cardiac anomaly. During the routine physical examination, a left scrotal tumor approximately 3 by 5 cm. was noted. History obtained from the parents indicated the tumor had been present since birth and had not changed appreciably in size. One month following recovery from a Blalock procedure, a left orchiectomy was done. Convalescence was uneventful.

The surgical specimen included the left testis and a short segment of spermatic cord. Attached to the upper pole of the testis, and included within the tunica albuginea, was a "bean shaped," dark red tumor measuring 3 by 5 by 2 cm. On sectioned surface, the tumor was well encapsulated, with small white bodies scattered throughout the otherwise firm, homogeneous, red tissue. The adjacent testis on sectioning showed soft, brown, tissue contained within the grey tunica albuginea.

Sections of the tumor showed splenic tissue with the usual fibro-muscular capsule and centrally projecting trabeculae. Lymphoid follicles with eccentrically placed arterioles were evident. Red blood cells were noted in the sinusoids. The adjacent testicular tissue was separated by only a small septum of fibrous hernia present, the testis and attached spleen having apparently negotiated the left inguinal canal without mishap. One case had a definite fibrous cord present, attaching a string of small accessory spleens to the parent organ. This finding is in agreement with most of the previously reported cases. The clinical features of this anomaly are difficult to assess since the reported cases are few indeed. The only acute symptoms are reported by Talman and by Settle[8] who observed two patients suffering with malaria. Pain and tenderness in the scrotal mass were noted during periods of exacerbation of their disease. From this consideration, one might theorize that changes would occur in ectopic scrotal splenic tissue in cases with leukemia, infectious mononucleosis, and familial hemolytic icterus. From the standpoint of differential diagnosis involving a testicular mass, the possibility of neoplasm makes surgical exploration of the scrotal contents mandatory. However, in cases with hypersplenism undergoing splenectomy, the awareness of this anomaly might well lead to a more favorable outcome.

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[1] Sneath, W. A.: J. Anat. and Physiol., 47: 340–342, 1913.

[2] Henke, F., and Lubarsch, O.: Handbuch Der Speziellen Pathologischen Anatomie Und Histologie. Band 1, Teil 2: 407–409, 1927.

[3] Talman, J. M.: Virchow's Arch., 259: 237–243, 1926.

[4] Olken, H. G.: Am. J. Path., 21: 81–85, 1945.

[5] Andrews, S. E. and Etter, E. F.: J. Urol., 55: 545–547, 1946.

[6] Tate, G. W. and Goforth, J. L.: Tex. State J. Med., 45: 570–572, 1949.

SUMMARY

Two cases of accessory splenic tissue located within the left scrotum are reported, bringing the total number of reported cases to thirteen.

The possibility of ectopic splenic tissue within the scrotum should be considered in cases presenting a scrotal mass.

[8] Settle, E. B.: Am. J. Surg., 50: 22–26, 1940.

nodules of accessory splenic tissue resembled beads on a string. At the level of the left internal inguinal ring, the fibrous cord became associated with the structures of the spermatic cord, terminating finally as a 2 cm., bluish-red tumor in the upper pole of the left testis. Grossly the grey tunica albuginea of the testis incorporated the blue tissue in the upper pole. On sectioned surface, the friable, brown, testicular tissue was evident (fig. 1, *B*). At the upper pole, and separated by a thin septum of fibrous tissue, was a circumscribed, well encapsulated, solid mass with a gross appearance strikingly similar to that of spleen.

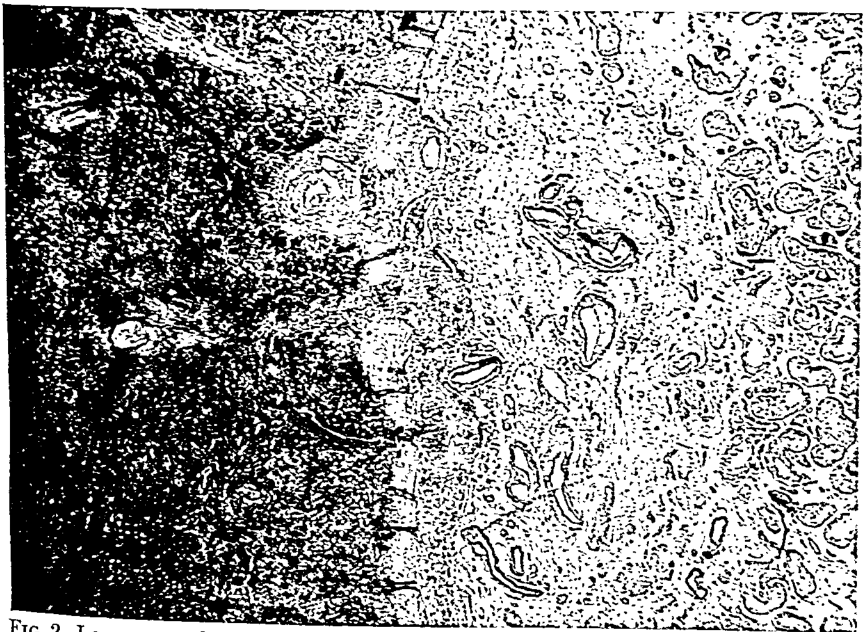

FIG. 2. Low power photomicrograph showing scrotal spleen attached to left testis. Note splenic capsule between spleen and testis.

Microscopic examination: The usual architecture of spleen and testis was evident on the same microscopic slide with only a thin intervening septum of fibrous connective tissue (fig. 2). The seminiferous tubules contained proliferating cells, but with few mature spermatozoa. Clumps of interstitial cells were present with their large, round, nuclei and pale, eosin-staining cytoplasm. The splenic portion showed a fibrous capsule with fibromuscular septa projecting inward. Red blood cells were noted in the sinusoids along with a considerable quantity of free blood pigment. The reticulum, malpighian bodies, and vessels showed no unusual features.

COMMENT

No attempt will be made to present the embryologic basis of the scrotal spleens described in these two cases. This aspect has been well covered in a report by Emmett and Dreyfuss.[7] In neither of our 2 cases was an associated inguinal

[7] Emmett, J. M. and Dreyfuss, M. L.: Ann. Surg., 117: 754–759, 1943.

"dyskeratosis." The latter consists of an imperfect and premature keratinization accompanied by variations in size, shape and staining intensity of adjacent nuclei. Fraser[4] states that the dyskeratosis is not an important feature because it is found in many skin diseases. Not all the surface cells are fully cornified in Bowen's disease; some retain nuclei that are surrounded by a clear space—the "corps ronds" of Darier. Occasionally isolated cell nests occur within the epithelium.[5] Scattered within the rete are clumps of nuclei, ranging from 2 to 12 in number, with a clear space at the periphery. Mitoses are frequent. The basement membrane may remain intact for a long time; and the intercellular bridges persist. The blood vessels within the corium are dilated and an infiltration of small round cells, chiefly lymphocytes and plasma cells, is present. Early Bowen's disease spreads in a lateral direction through metaplasia of adjacent normal cells rather than by penetration into the surrounding healthy epidermis.[6]

Bowen's disease of the skin may at any time change into frank and grossly obvious epithelioma.[7] The latent period however may be a long one, as much as 30 years[8–9] elapsing between onset and invasion. Fraser,[4] on the other hand, emphasizes that from the beginning the cellular changes in Bowen's disease are characteristic of malignancy, the lesion being pathologically malignant in spite of what appears to be a benign clinical course. Metastases have been demonstrated even where there was no gross evidence of malignant change in the primary lesion.[10] Some authors[11] maintain that this lesion can metastasize without invading the basement membrane. Stout[10] points out that metastasis is impossible unless penetration has occurred at some point. The break through is usually of microscopic size and easily missed unless careful serial sections are made. Figure 1 from a patient with Bowen's disease of the renal pelvis (case 1) clearly shows the tiny point of invasion. It is of interest to note that a process similar to Bowen's disease is often seen at the margin of a clinically frank carcinoma.[12]

In our series of 30 cases, Bowen's disease was frequently the initial lesion, but on occasion it preceded or was associated with or followed a papilloma or papillary carcinoma or squamous cell epithelioma. The presence of Bowen's disease overshadowed any benign process; this was proven by the subsequent clinical course.

Stout[10] notes that the lesions of Bowen's disease may follow one of two courses:

1. The component cells may multiply, heap up and form a tumor nodule which may either fungate or ulcerate and thus simulate the usual squamous cell epithelioma. This type tends to infiltrate locally instead of metastasize.

2. The cells may continue to reproduce the poikilocarynosis (nuclear varia-

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[4] Fraser, J. F.: Arch. Dermat. and Syph., **18:** 809, 1928.

[5] Brighton, G. R. and Altmann, F.: Arch. Otolaryng., **36:** 254–271, 1942.

[6] Montgomery, H.: Arch. Dermat. & Syph., **39:** 387–408, 1939.

[7] Jeffcoate, T. N. A., Davie, T. B. and Harrison, C. V.: J. Obst. & Gyn. Brit. Emp., **51:** 377–385, 1944.

[8] Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co., 1940.

[9] Wise, G.: Am. J. Ophth., **26:** 167–171, 1943.

[10] Stout, A. P.: N. Y. State J. Med., **39:** 801, 1939.

[11] McGavic, J. S.: Am. J. Ophth., **25:** 167–176, 1942.

[12] Novak, E.: Gynecological and Obstetrical Pathology. Philadelphia: W. B. Saunders Co., 1947.

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INTRA-UROTHELIAL CANCER: CARCINOMA IN SITU, BOWEN'S DISEASE OF THE URINARY SYSTEM: DISCUSSION OF THIRTY CASES

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The gross physical characteristics of the majority of malignancies that arise from the surface of the body, or from the interior lining of a hollow viscus, are well known and recognizable. There are the relatively common papillary tumors and then again the fairly frequent nonpapillary or flat indurations with or without a crater-like center. There are however other lesions less common whose gross features are inconspicuous and seemingly benign but whose microscopic picture is that of malignancy. They may appear as persistent small single or multiple papules, or as a small area of ulceration, or merely as a tiny focus of redness or discoloration. The group includes: carcinoma in situ, intra-epithelial (urothelial) cancer, Paget's disease, erythroplasia of Queyrat, a variety of dyskeratoses and hyperkeratoses, and Bowen's disease. Some of these names are synonyms, some present minor clinical variations, some have a predilection for a particular site on the human body and some show a moderate variation in the histologic pattern. They all however possess one common denominator: the microscopic picture is that of malignancy and all are potentially invasive. The clinical evidence is minimal, and there is an erroneous notion that a diagnosis of Bowen's disease denotes a precancerous lesion or one whose malignancy is doubtful. These two factors tend to lull the examining physician into a state of watchful waiting and the surgeon into performing an inadequate operation. The end results of such procedures, have, in many instances, been disastrous. It is our purpose in this article, to call attention to these clinically deceptive lesions, to emphasize that they are malignant from onset, that they can be highly invasive and that only early adequate eradication can hold the promise of cure.

In 1912, Bowen described the disease which now bears his name.[1] He looked upon the lesions as precancerous affections of the skin only, but it has now been demonstrated that the process can also involve mucous membranes. The cutaneous form of Bowen's disease is characterized by discrete or confluent, flat or slightly elevated papulosquamous patches with serpiginous or circinate border. The skin induration is minimal. The crusts remove easily to leave a dull red smooth moist surface with pin-point pearly elevations[2] which bleed easily. Microscopically the cutaneous lesions show an abrupt change from normal skin to the diseased area, with well defined, often clubbed and edematous rete pegs. There is hyperplasia of the epidermis with a phenomenon called by Darier[3] similar in appearance to acute diffuse eczema. It may exude a copious clear yellowish secretion. Histologically, the so-called Paget's cells are seen in the epidermis. These cells are large, round or oval, and have an abundant lightly acidophilic cytoplasm. They contain large vesicular or hyperchromatic nuclei with large nucleoli.[13] Mitoses are present. The surrounding epithelium is compressed. Intercellular bridges are not seen in the epidermis of Paget's disease, but are present in the cutaneous forms of Bowen's disease. Erythroplasia of Queyrat, the second of this clinically enigmatic triad, has been described as being reddish in appearance, somewhat raised above the surrounding surface, and being composed of single or multiple papules that are confluent. Microscopically, there is hyperplasia of all the layers and an increase and engorgement of subcutaneous capillaries. The margins are usually sharp and an eczematoid appearance is usually present.[14] It will be noted from this description that the clinical appearance of erythroplasia is quite similar to that of the other two components of the triad. Histologically there is a difference between erythroplasia on the one hand and Bowen's and Paget's diseases on the other. Erythroplasia is apparently a benign lesion.[15] Many dermatologists, however, state that erythroplasia eventually can become malignant, at which time the histological appearance becomes like that of the other intraepithelial cancers. It is for this reason that some look upon erythroplasia as a slow form of Bowen's disease. The histologic characteristics of Bowen's disease have already been described.

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[1] Bowen, J. T.: J. Cut. Dis. Incl. Syph., 30: 241–255, 1912.
[2] Knight, R. van D.: Am. J. Obst. & Gyn., 46: 514–524, 1943.
[3] Darier, J.: Ann. de Dermat. & Syph., 1: 49–61, 1920.

The lesions caused by syphilis may be differentiated microscopically by demonstrating endothelial thickening and perivascular cellular infiltration. Serologic tests and therapeutic response to antibiotics are additional aids in the differential diagnosis. Seborrheic keratosis and basal cell epithelioma show significant clinical and microscopic differences.

BOWEN'S DISEASE OF MUCOUS MEMBRANES

Jessner,[16] in 1921, was the first to report a case of Bowen's disease of the mucous membranes. Stout[10] in 1939 reviewed 32 patients with Bowen's disease whose lesions showed signs of clinical malignancy. In 12 patients the mucous membrane was the primary site. He called attention to an invasion rate of 40 per cent in patients with mucosal involvement as compared with only a 2–3 per cent incidence in the much more frequent skin lesions. Cipollaro and Foster,[17] in 1940, discussed 50 mucous membrane case reports which they had found in the literature, and they added two of their own. They found that the disease had involved the glans penis, lip, vulva, vagina, tongue, nares, uvula, vocal cord, palate and tonsils. Both cases which Cipollaro and Foster[17] reported gave a history of having received arsenical treatment. A number of previously reported cases also had had arsenotherapy, but this did not occur with sufficient regularity to enable one to draw a definite conclusion as to a possible etiological role of the tion in size and shape) of the original lesion and differ thereby from the classic types of epidermoid epitheliomas. This group includes the typical Bowen epitheliomas whose course was first described by Darier.[3]

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[13] Moore, R. A.: Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1944.
[14] Queyrat, M.: Bull. Soc. Franc. Derma. et Syphill., **22:** 378–382, 1911.
[15] Melicow, M. M. and Ganem, E. J.: J. Urol., **55:** 486–513, 1946.
[16] Jessner, M.: Arch. f. Dermat. u. Syph., **134:** 361–369, 1921.
[17] Cipollaro, A. C. and Foster, P. D.: N. Y. State J. Med., **40:** 264–275, 1940.

Wise[9] states that the lesion of Bowen's disease may develop into either a squamous cell or basal cell epithelioma, or a mixture of both. Stout, however, is of the opinion that only a squamuos cell epithelioma can form. Montgomery[6] concurs with Stout that Bowen's disease is from the start a squamous cell lesion, and that it never changes into a basal cell carcinoma.

Bowen, in his original report,[1] mentioned other skin lesions which he considered as being "precancerous." They were cornu cutaneum, Paget's disease of the nipple, senile keratosis, xeroderma pigmentosum, arsenical cancer, chimney sweep's cancer, cancer in workers in paraffin and tar, x-ray dermatitis, and leukoplakia. These conditions have in common a slowly increasing epithelial hypertrophy, hyperkeratosis (except Paget's disease), pronounced proliferation of the rete Malpighii accompanied by changes in nuclear appearance and vacuolization and degeneration in the epithelial cells. Erythroplasia of Queyrat may also be included in this group.

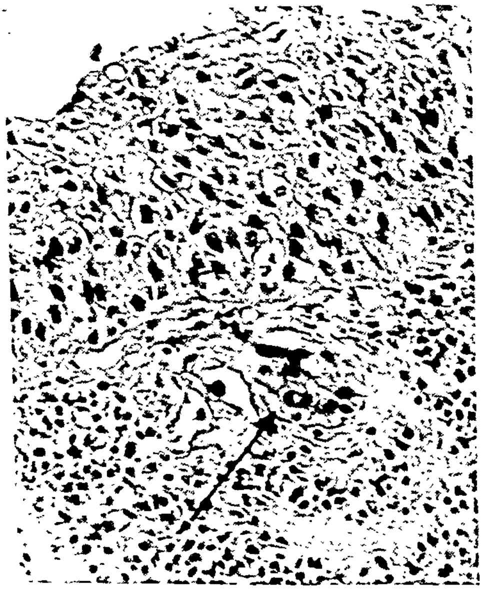

FIG. 1. Case 1. Intra-urothelial epithelioma of renal pelvis (Bowen's disease). Note invasion into submucosa.

There are three lesions, Paget's disease, erythroplasia, and Bowen's disease, which interest the urologist because of their occurrence on the penis. There is considerable disagreement amongst pathologists and dermatologists regarding the differences between these three lesions, and as a result much confusion has developed in the minds of urologists. According to some pathologists, extramammary Paget's disease does not exist. Those who do accept the existence of true Paget's disease on the penis describe the lesion as florid, intensely red and raw,

DISCUSSION OF CASES

The first case concerns a 67-year old white man who had undergone a transurethral resection of the prostate 6 years, and a suprapubic prostatectomy 4 months before being readmitted for what was later diagnosed as Bowen's disease of the kidney. It is therefore difficult to estimate the duration of symptoms that were caused by the kidney lesion. The patient complained of right flank pain and of tenderness over the lower pole of the right kidney. Pyelography revealed a a contracted right renal pelvis and dilated calyces. The symptoms, findings and pyuria were suggestive of right chronic pyonephrosis. Microscopic sections of the excised kidney revealed an infiltrating malignancy (fig. 1) arising from a "carcinoma in situ" that developed in the urothelium. It reveals a microscopic finger-like mass of cancer cells which had pierced the otherwise intact basement membrane at a single point. This is believed to be the site or one of the sites from which the malignancy escaped from the urothelial confines and inundated the kidney.

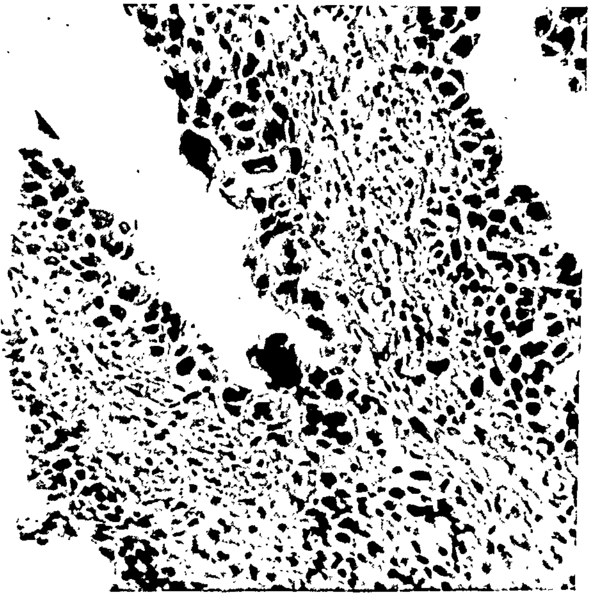

FIG. 2. Case 2. Intra-urothelial epithelium of ureter (Bowen's disease). Note clumping of nuclei and deep-staining.

In case 2 the patient underwent a left nephrectomy for papillomatosis of the pelvis which contained areas of questionable early malignancy. The patient returned 4 years later because of gross hematuria which emanated from the ureteral stump. The latter was removed and serial microscopic sections showed an intraurothelial epithelioma or Bowen's disease (fig. 2) with areas of infiltration. The presence of papillomatosis in one area of the urologic tract and a carcinoma in situ in another is worthy of mention.

Six patients of the series may be considered to have had inadequate therapy after the diagnosis of Bowen's disease was made. One of the patients (case 6) died of carcinomatosis following a 6 year history of recurrent bladder tumors.

arsenic.[8] Of the 30 cases presented in this review, 10 per cent gave a history of arsenotherapy. Cipollaro and Foster noted that Bowen's disease of the mucosa occurred with somewhat greater frequency in the female. The age incidence in their series was from 23 to 81 years, with an average of 51. They cite Michel's (1929) classification of the various stages in the development of Bowen's disease of mucous membrane which is as follows:

(1) Early stage: The lesions are reddish, well-circumscribed, glossy, slightly infiltrated, painless and not ulcerated. Frequently they are covered with a heavy scale. The base of the lesions is soft. Slight pruritis may be present.

(2) Latent stage: Changes in the aforementioned lesion may occur slowly. It may become nodular or papillomatous with or without a crust. The base becomes infiltrated. There is a tendency to acuminatization and ulceration.

(3) Late stage: The nodular or papillomatous areas may ulcerate. Deep infiltration of the base develops. Regional lymph glands may become involved and distant metastases may then occur.

The essential histologic features are the same in both skin and mucous membrane lesions of Bowen's disease. Hyperkeratinization is less pronounced in the mucous membrane lesions. Stout[14] points out that the microscopic picture of mucosal Bowen's disease is not as clear as in skin lesions, and further, unless poikilokaryonosis (nuclear variation in size and shape) is present, a diagnosis of this lesion is not valid.

We are presenting 30 cases of intra-urothelial cancer (Bowen's disease, carcinoma in situ) from the files of the Squier Urological Clinic of the Presbyterian Hospital, New York City. In only 1 case was there involvement of the renal pelvis, two involved the ureter, seventeen the bladder, five the urethra, and five the penis. The ages ranged from 31 to 77, averaging 64 years. There were 5 Negroes and 25 white patients. Eight were female and twenty-two were male. It is difficult to accurately estimate the time of onset of urinary symptoms in this age group. Their duration prior to making a diagnosis of Bowen's disease ranged from 2 days to 10 years, with an average of about 2 years.

As just noted, the largest number of cases of mucosal Bowen's disease were those which involved the bladder. In those patients in whom the lesion was not associated with an obvious neoplasm, it was variously described as follows: "granular lesions partially covered with calcific crusts," "reddened elevated patch on postero-lateral wall," "ulcer," "slough," "raised area," "crater-like ulcer," etc. The lesions were estimated at from 1 to 3 cm. in diameter. In a number of cases the area was associated with an apparent neoplasm. An isolated area of Bowen's disease in the urinary bladder can give great difficulty in differential diagnosis. It can resemble focal acute or chronic cystitis, focal follicular cystitis, Hunner's ulcer, or the white opaque plaque of leukoplakia. Histological features of the latter are an orderly urothelial hyperplasia, squamous cell metaplasia and surface keratinization. Histological findings in all the aforementioned lesions are distinct, and they are easily differentiated from intra-urothelial cancer. Adequate biopsy is essential for the diagnosis of Bowen's disease.

the penis (figs. 4 and 5). Unfortunately he was treated by partial amputation only, and 3 years later clinical evidence of advanced carcinoma appeared and microscopic sections of the deep inguinal nodes showed diffuse invasion by an anaplastic carcinoma.

Eight of the cases are being followed and some may become candidates for radical surgery. One patient, case 4, suffered from recurrent bladder papillomas which were fulgurated over a period of 7 years. At the end of this time an area of Bowen's disease was found and it too was treated by fulguration. Three years later a grossly obvious malignancy was discovered on cystoscopy. The sequence of events in case 5 parallels that described in case 4. Another patient, case 10, a 77-year old white man, had symptoms of urinary obstruction and infection for 5 years. The first biopsy revealed cystitis cystica; later a papillary tumor was fulgurated. The latest biopsy showed an intra-urothelial epithelioma (fig. 6). Cases 13 and 14 present the histories of two elderly men who had recurrent bladder lesions which proved to be Bowen's disease. In each a grade 2 epithelioma subsequently developed. Similarly another patient, case 19, who first had bladder papillomas later developed Bowen's disease and finally papillary carcinoma. A patient with Bowen's disease of the penis, case 26, underwent partial amputation of the glans. A recurrence two years later was treated with radium because the patient refused radical surgical treamtent (fig. 7). In view of the explosive potentialities of intra-epithelial cancer it will be necessary to follow this patient carefully. Case 27 also illustrated the progressive course of Bowen's disease. Seven years prior to the last examination the patient had Bowen's disease of the preputial region of the penis. A circumcision was performed. Four years later, a

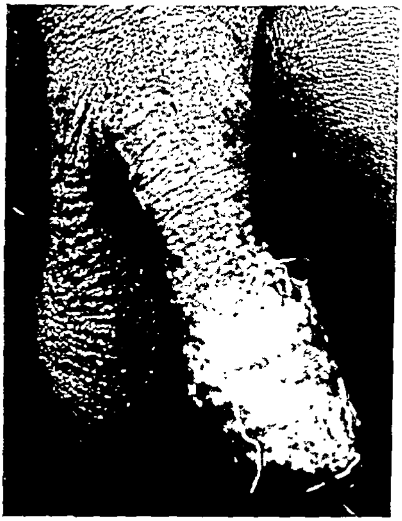

Fig. 4

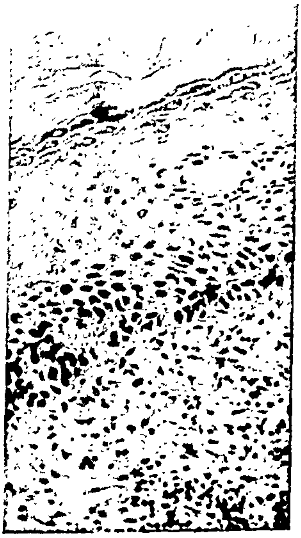

Fig. 5

Fig. 4. Case 30. Clinical picture of intra-urothelial epithelioma of glans penis (Bowen's disease).

Fig. 5. Case 30. Intra-urothelial epithelioma of glans penis (Bowen's disease). Lesion recurred and metastasized to inguinal glands.

The initial lesion, a papillary carcinoma of the bladder, was removed by partial cystectomy. Three years later a new lesion was biopsied and found to be Bowen's disease. It was fulgurated but it soon recurred and diffusely involved the bladder. Fulguration was insufficient to halt or eradicate the disease.

In case 12 the patient entered the hospital with symptoms of only 1 month's duration. Biopsy of the bladder revealed Bowen's disease (fig. 3). A severe infection necessitated chemotherapy and surgical treatment was delayed 4 months. At the end of this time exploration revealed an inoperable carcinoma. Another patient, case 16, underwent a nephrectomy for hydronephrosis. The ureter was not completely removed. Two years later the patient died from generalized carcinomatosis and the post-mortem examination revealed the primary site to be in the ureteral stump. The patient, in addition, had a carcinoma of the bladder with areas of Bowen's disease. One patient, case 18, who had Bowen's disease of the bladder, was treated with radium. The malignant potentialities of the disease are exemplified by the death of this patient 4 years later from generalized carcinomatosis. Operation on a patient, case 28, with a clinically doubtful lesion on the glans penis was delayed only 3 weeks after a biopsy revealed Bowen's disease; yet the excised organ and lymph nodes already revealed a diffuse invasion and the patient died of carcinomatosis 6 years later. The original biopsy compared with the operative specimen showed a distinct change in the appearance of the tumor process. Another patient, case 30, also suffered from Bowen's disease of

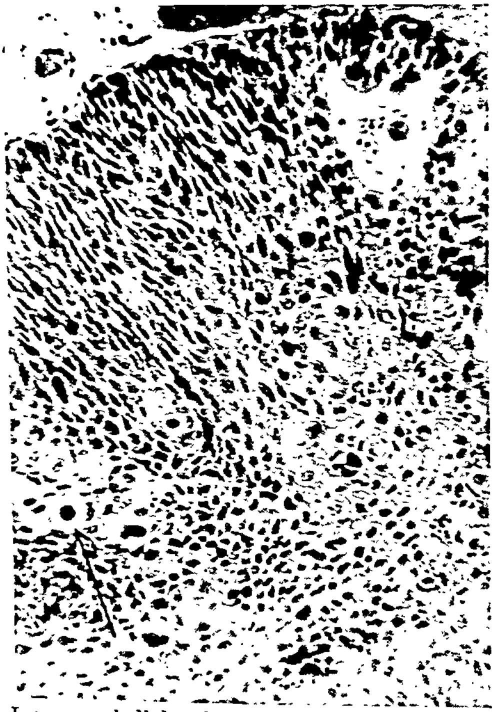

FIG. 3. Case 12. Intra-urothelial epithelioma of urinary bladder (Bowen's disease). Lesion is limited to urothelium. Note "corpe ronds." Patient later showed grade 4 anaplastic infiltrating epithelioma.

pubic prostatectomy was performed. Sections showed a benign gland but the posterior urethra and suburethral glands were the seat of Bowen's disease. The last, case 25, underwent a total cystectomy including prostatectomy for infiltrating carcinoma of the bladder, and on section the specimen revealed an intra-urothelial carcinoma of the posterior urethra, quite different in appearance from the bladder tumor.

TREATMENT

The majority of our cases of Bowen's disease were inadequately treated—the result of a tendency to regard the lesion as precancerous or of doubtful malignancy. Clinically the lesions do appear equivocal, causing the surgeon to adopt a conservative attitude. Watchful waiting, half-way measures are the rule and in the meantime the disease progresses. Emphasis must be placed on the fact that Bowen's disease is cancer and that it can spread rapidly, particularly after disruptive inadequate procedures.

Intra-urothelial cancer has been attacked in several ways. One of the favorite weapons is radiation therapy. Two of our patients were apparently cured with radium (cases 20 and 21) but the use of this agent in Bowen's disease of the urothelium is not generally recommended. Jeffcoate[7] and co-authors reported 2 cases in which the vulva was involved and in which the lesions were not arrested by radium implantation. Montgomery,[6] in discussing the cutaneous type of Bowen's disease, points out that it tends to simulate malignancy resulting from radiotherapy. He therefore considers it illogical to treat this disease with either radium or x-ray. Stout[10] also discourages the use of chemicals or radiation. Cauterization may in isolated early cases be effective, but it should be used with caution because it too may augment the malignant spread.[11] Surgery is therefore recommended as the treatment of choice. Bowen[18] in 1915 advised thorough excision or complete destruction of the lesion. In the darkness of our current ignorance of cancer our most effective procedure is complete excision, a procedure recommended by Bowen 26 years ago.

CONCLUSIONS

The problem of carcinoma in situ (Bowen's disease) is discussed. Thirty cases of involvement of the mucous membranes of the urinary system are presented.

Bowen's disease is an intra-epithelial cancer that can occur in the skin or mucous membrane.

The term Bowen's disease is often used synonomously with intra-epithelial (urothelial) cancer and with carcinoma in situ.

The degree of invasiveness and rapidity of spread varies considerably in intra-epithelial cancer. It is for this reason that the lesion in many of the patients was erroneously termed "precancerous."

Palliative measures, inadequate removal, and watchful waiting, as with all cancer, can prove disastrous.

The most effective therapy is complete surgical excision or thorough fulguration. Choice of procedure depends on the location and physical characteristics of the lesion.

[18] Bowen, J. T.: J. Cut. Dis., **33:** 787-802, 1915.

recurrence developed which was treated with radiotherapy. Another recurrence, within a year, required amputation.

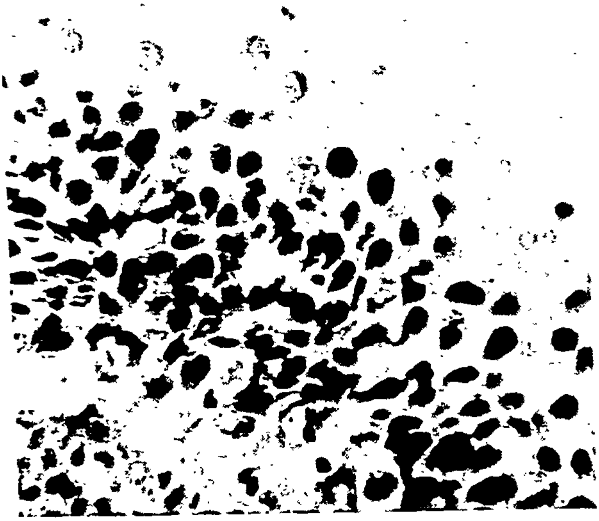

FIG. 6. Case 10. Intra-urothelial epithelioma of urinary bladder (Bowen's disease). Note deep-staining of nuclei.

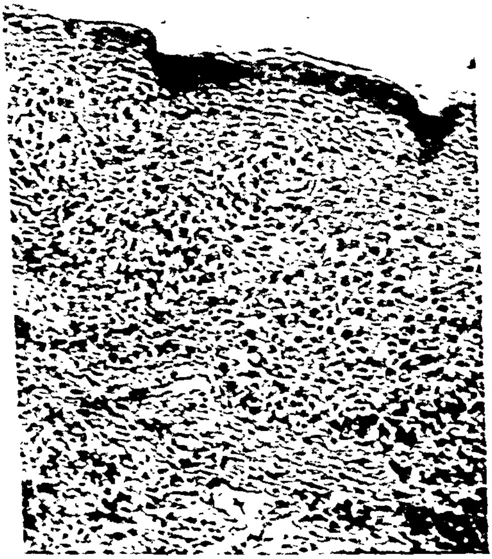

FIG. 7. Case 26. Intra-urothelial epithelioma of glans penis (Bowen's disease). Lesion recurred in 20 months.

In 3 patients intra-urothelial cancer of the posterior urethra was discovered as an incidental finding following prostatectomy. The first, case 22, underwent suprapubic prostatectomy, and microscopic examination of excised urothelium revealed the changes characteristic of Bowen's disease. The second, case 23, was preoperatively suspected of having a prostatic malignancy and a radical retro-

In one instance a patient who had benign prostatic hypertrophy which was relieved by transurethral resection with good results and no residual urine suddenly had trouble voiding several months after operation. In going over the patient's history it was discovered that his local physician, in another state, had started him on banthine for ulcer the week before his recent difficulty in voiding started. He was advised to discontinue banthine and his urinary symptoms promptly disappeared.

Table 1 shows the premedication condition of these 10 patients on admission and the results following discontinuance of banthine and catheter drainage. It will be noticed that six of the 10 patients were able to void while four required operation.

It becomes evident that the male ulcer patient with early prostatic hypertrophy in whom complete urinary retention develops may have this retention as a result of banthine.

It is well worthwhile to check the residual urine as a matter of routine on this class of ulcer patient before starting ulcer management. In this way one is in a better position to evaluate the patient, should urinary retention occur.

SUMMARY

The elderly male ulcer patient with early prostatic hypertrophy may develop complete urinary retention while on banthine therapy.

In some cases complete urinary retention may be relieved by discontinuance of the drug and by catheter drainage for a few days while other patients may require operation.

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URINARY RETENTION DUE TO BANTHINE

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During the past year there has been widespread use by gastro-enterologists of banthine for the treatment of peptic ulcers. Since many of these ulcer patients are men in the prostate age group, it becomes important that the urologist understands the action of this drug on the bladder.

Banthine bromide is a brand of methantheline bromide. Chemically it is a quaternary amine and its formula is B-diethylaminoethyl xanthene-9-carboxylate methobromide. This drug belongs to the class of parasympathetic blocking agents. When given in the usual dosage it exhibits two principal types of action. The first is an atropine-like action and the second is an autonomic ganglion blocking action. Its action as a ganglion blocking agent on the parasympathetic system, resulting in urinary retention in the occasional patient with early prostatic hypertrophy should be kept in mind.

Table 1

CASE	AGE	RECTAL EXAMINATION	PREMEDICATION RESIDUAL	POSTMEDICATION RESIDUAL	RESULTS AFTER DRUG DISCONTINUED
1	54 yrs.	Grade 1 benign	None	Complete retention	Voided with no residual
2	61 yrs.	Grade 2 benign	3 oz.	Complete retention	Required T.U.R.
3	58 yrs.	Not enlarged benign	None	Complete retention	Voided with no residual
4	66 yrs.	Grade 3 benign	1 oz.	Complete retention	Required T.U.R.
5	71 yrs.	Grade 1 benign	2 oz.	Complete retention	Voided with 2 oz. residual
6	69 yrs.	Grade 1 benign	None	Complete retention	Voided with 1 oz. residual
7	65 yrs.	Grade 1 benign	½ oz.	Complete retention	Voided with ½ oz. residual
8	74 yrs.	Grade 2 benign	2 oz.	Complete retention	Required T.U.R.
9	54 yrs.	Not enlarged benign	None	Complete retention	Voided with no residual
10	77 yrs.	Grade 3 benign	3 oz.	Complete retention	Required T.U.R.

During the past year I have seen 10 patients with urinary retention which I believe was precipitated by banthine therapy. All were ulcer patients and had various degrees of prostatic hypertrophy. However, they had been voiding fairly well and never had urinary retention up to the time banthine was started. Several patients had complained of previous symptoms of prostatism, although the symptoms had been mild in each case. While we appreciate the fact that any of these patients could have developed a complete urinary retention while in the hospital on any type of ulcer management, yet it hardly appears likely that such a coincidence would occur. Our medical service has not had this experience during the past 30 years of ulcer treatment.

in the known conception group is illustrated in table 3, together with the initial sperm count prior to stilbestrol.

Through personal communication, I know of two additional conceptions, one a patient of Dr. Joseph Kiefer's (infertile marriage of 2½ years), and the other a patient of Dr. Rudolph Hack's (infertile marriage of 4 years), both conceptions occurring during the third month of 0.2 mg. stilbestrol daily.

The initial counts in this series are given in table 4.

TABLE 1. *Average number of counts after institution of stilbestrol (in addition to the initial)*

13 — 1
26 — 2 to 7 (av. 3)
1 — none

TABLE 2. *Change in count after administration of stilbestrol*

Increase	20
Decrease	7
No change	12

TABLE 3. *Known positive conceptions*

PATIENT	INITIAL COUNT MIL./CC	DURATION OF INFERTILE MARRIAGE IN YEARS
1	1	2
2	68	3
3	20	6
4	69	1.5
5	2	2
6	10	7
7	20	8.5
8	16	3

TABLE 4. *Counts*

Spermatozoa/cc	*No. pts.*
Less than 10,000,000 (8 below 1,000,000)	12
10–25,000,000	13
More than 25,000,000 (only 6 above 60,000,000)	15

Twelve are cases of extreme oligospermia of less than 10 million sperm per cubic centimeter, of which 8 were less than 1 million, many on the order of about 1 spermatozoa per high power field of the usual cover slip preparation, 13 between 10 and 25 million and 15 more than 25 million with only 6 above 60 million. I have the impression that the lower the count, the less likely there is to be a stimulation or increased count with stilbestrol and especially so below 10 million.

Whether there is a persistence of increased counts after discontinuance of stilbestrol would seem of some interest, and I re-submit the slide presented at Milwaukee last year of the first known conception after stilbestrol (table 5). I

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INFLUENCE OF SMALL DOSES OF STILBESTROL ON OLIGOSPERMIA

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On analyzing this series of 40 patients, it became evident that it is not an exact report on stilbestrol alone, but rather its combination with other medicaments. In a previous series of approximately the same number of patients I was impressed by the statistical analysis of follow-up questionnaires that B_{12} was of some value in infertile marriages when given parenterally in a dosage of 50 to 100 micrograms weekly. Generally with stilbestrol, B_{12} has been given orally and I now believe B_{12} is not as effective orally as when given parenterally, so probably the results as presented are largely due to stilbestrol. Also thyroid extract has been administered when the B.M.R. was on the minus side, and generally some "over all" vitamin mixture. The only omission has been that of products commonly used for infertility, namely, chorionic gonadotrophic hormones, pregnant mare serum and allied substances. I do not wish to imply that such products may be useless in some instances of oligospermia. From questionnaires over the past several years it was noticed that conception occurred sometimes following discontinuance of pituitary hormones by a delayed period of one to two years. It is accepted, I believe, that large dosage of chorionic gonadotropin may, in some patients, further increase oligospermia. It is possible that this in turn may be followed by a rebound phenomenon like that following testosterone administration, as described by Heller, Heckel and McDonald.

The only reference that I have seen on the use of estrogens for infertility of the male is that of Culp and Beynon in their excellent report. They reported one instance in which there was a decreased sperm count during thyroid and vitamin E therapy. There was a return to normal after progynol administration and about 4 months subsequently successful impregnation.

In the present series of 40 patients, counts were made, with one exception, in all, subsequent to the initial count and stilbestrol administration (table 1).

In rating the effect on sperm counts, division was made into 1) increased counts, 2) decreased, and 3) no change, with reasonable allowance for normal variations.

It will be noted in table 2 that in 20 there was an increase, in 7 a decrease, and in 12 no change. It was significant that the "no change" included a preponderance of those with marked oligospermia, such as less than 10 million sperm per cubic centimeter. The most striking change occurred in those with the least oligospermia such as 50 to 90 million with intermediate 20 to 50 million likely to go either way.

Conception occurred in 8 of the series with 23 known to be negative and 9 unknown (table 3). This percentage is not impressive, but the period of observation covers 1 year with an average of 6 months. The period of infertile marriage

It is generally recognized that a certain number of patients with lowered fertility will eventually impregnate without any treatment, even those with marked oligospermia, such as below 10 million. I do not think, however, that there is a marked variation in subsequent counts within a reasonable period of time, providing the whole ejaculate has been obtained and there have been 4 or more days of abstinence before collection of the specimen. This seems especially true of patients with oligospermia below 60 million per cubic centimeter.

The preponderance of the more extreme oligospermias in this series is based on the assumption that there is very little to lose with a new procedure in this type of patient. Finally the observations are presented without implying that stilbestrol in small doses is the cure-all for infertility in the male, but rather as an interesting lead, worth pursuing further.

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had an opportunity to examine the semen of this patient 1 year later, and there was a drop from 102 million at or about the time of conception to 59 million, 11 months later. In a few other instances we have noted a decrease in shorter intervals after discontinuance, but seldom to that prior to stilbestrol.

In regard to the optimum dosage of stilbestrol, there have been about an equal number of patients to whom stilbestrol has been administered in a dosage of 0.1 mg. daily and 0.2 mg. daily. Favorable and unfavorable responses have followed both schedules. Two instances of gynecomastia developed after a few weeks on 0.2 mg. daily, which we believe at this time is an indication for discontinuing the drug, at least for stimulating purposes. There has not been any known instance of gynecomastia on 0.1 mg. daily and no complaints of decreased potency on either schedule. One would likely get a more prompt answer from the larger dosage as to the three types of response tested above: increase, decrease or no change. At present, however, we are inclined to an initial dosage of 0.1 mg. daily and regulating a change or stopping the drug according to the findings of the subsequent specimens. Prescriptions should be marked "no refill" unless stilbestrol is dispensed. Should future observations reveal that with decrease there is a favorable rebound reaction after discontinuance, like that described by Heller and Heckel, following testosterone, a different regimen would be indicated in this type of response. At present, we do not advise administration longer than 4 months, with check-up of semen specimens every 4 to 6 weeks during the administration of stilbestrol.

TABLE 5

D. M. Age 29. Barren 8 years before stilbestrol. Count was 12,000,000, 80 per cent nonmotile, 30 per cent abnormal forms.

After stilbestrol: count	
6 weeks after	41,000,000
12 weeks after	52,000,000
18 weeks after	102,000,000
Conception at 16 weeks.	
Spermatozoa count 11 months later	59,000,000

It may be found in the long run that it will be a better procedure to give intermittent courses each month for 2 weeks prior to the expected ovulation of the wife. One patient, not included in this series, had an initial count of 197 million with a quantity of 2 cc and rather high viscosity. Stilbestrol was administered with the thought that it might increase the quantity and decrease the viscosity. Seven weeks later the count reached 1,000 million per cubic centimeter. In the 1 patient included in this series without a subsequent count, conception occurred about 2 weeks after the institution of stilbestrol. This was an infertile marriage of 6 years. At present the method of intermittent administration is being used for those with counts from 50 to 100 million when there is other evidence of lowered fertility.

been found to be the main components of the adrenal venous blood of the dog.[8] Perfusion of isolated beef adrenals has shown that these two compounds are present in large amounts and that 11-dehydrocorticosterone, 11-desoxycorticosterone, and cortisone are found in smaller amounts along with several unknown compounds.[6] ACTH added to the perfusate increases the production of of these components many times during a given period. The addition of 11-desoxycorticosterone and 11-desoxy-17-hydroxycorticosterone to the perfusate showed that these compounds were converted by the adrenal to corticosterone and 17-hydroxycorticosterone respectively. Estrogens and androgens may be synthesized by the adrenal but there is as yet no direct evidence of this process, although they can be isolated from adrenal tissue.

After being metabolized in the body, the adrenocorticoids appear in the urine as 17-ketosteroids and corticoids. In men a certain proportion of the 17-ketosteroids are derived from testis precursors, but about three-fifths come from metabolites of the adrenal cortex.[9, 10] In women practically all the urinary 17-ketosteroids are derived from adrenal steroid metabolites. Both the 17-ketosteroid and the corticoid urinary levels reflect in general the functioning ability of the adrenal gland. Thus in Cushing's syndrome there is usually, but not consistently, an increased excretion of 17-ketosteroids particularly in patients with adrenal hyperplasia or malignant tumors.[11] The measurement of urinary free corticoids by the formaldehydogenic method has not shown levels consistent with the clinical findings in our patients manifesting adrenal hyperfunction.[12]

Hypersecretion of the adrenal 11-oxysteroids, particularly corticosterone and 17-hydroxycorticosterone, are believed to account for most of the pathologic and physiologic alterations occurring in Cushing's syndrome.[3] Hypersecretion of adrenal steroid metabolites resembling androgens would account for the hirsutism, acne, enlarged clitoris, and other features occasionally found in women who have features of both Cushing's syndrome and the adrenogenital syndrome. The imbalance in production of these two groups of adrenal steroids accounts for the variability in the clinical picture of these patients as well as the inconsistent pattern of both urinary 17-ketosteroid and corticoid excretion.

Pathology: The disturbance initiating adrenal cortical hyperfunction has not been established. It is probably hormonal and may arise from the hypothalamus, the pituitary, or the adrenal gland. Certain brain stem tumors can cause various endocrine symptoms in children, presumably by stimulation of the adjacent pituitary.[13, 14] Recent experimental work[13a, 15] has shown that selective lesions

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CUSHING'S SYNDROME

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The term "Cushing's syndrome" refers to the clinical picture described originally by Harvey Cushing as pituitary basophilism.[1] Unless induced by treatment the syndrome is caused in all instances by hyperadrenocorticism, the disorder originating in the adrenal or occurring secondary to another stimulus. The term "Cushing's disease" is restricted usually to the few cases of Cushing's syndrome associated with a basophilic adenoma of the pituitary gland, assumed by some to be the source of adrenal cortical stimulation.

The pathologic and metabolic changes present in patients with Cushing's syndrome are the result of an excess of adrenal 11-oxysteroids. Most of these changes can be produced by the administration of ACTH,[2] which stimulates, among other things, the output of the 11-oxysteroids, or by the administration of 17-hydroxydehydrocorticosterone (cortisone, compound E)[3] or 17-hydroxycorticosterone (compound F).[4]

Cushing's syndrome is much more common in women than men, and is seen occasionally in children. The life span of these patients is shortened. The characteristic clinical features of the syndrome are described later in the section on diagnosis. In many patients the complete clinical picture does not develop or it may be mixed with features of the adrenogenital syndrome.

PHYSIOLOGY

Only a brief outline of adrenal cortical physiology will be given here; a thorough presentation of this subject in the form of a symposium appeared recently.[5] Adrenal cortical function includes three major parts: 1) maintenance of the electrolyte balance by regulation of sodium, potassium, and water excretion; 2) regulation of carbohydrate, fat and protein metabolism; 3) androgenic effects including somatic and sexual development. Estrogenic and other adrenal functions need not be considered here.

About 30 adrenal steroids have been isolated, but of these only 6 are capable of maintaining life in the adrenalectomized animal.[6] These are corticosterone, desoxycorticosterone, dehydrocorticosterone, 17-hydroxycorticosterone, 17-hydroxydesoxycorticosterone and 17-hydroxydehydrocorticosterone. The probable precursor of adrenocorticosteroids is cholesterol as shown by perfusion of C-14 labeled cholesterol through isolated adrenals following which C-14 containing corticosteroids are obtained.[7] Corticosterone and 17-hydroxycorticosterone have by ACTH or cortisone therapy[20, 21] and lend support to the belief that primary adrenal cortical hyperfunction may cause basophilic adenomas and Crooke's changes of the basophil cells.

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[2] McAlpine, H. T., Venning, E. H., Johnson, L., Schenker, V., Hoffman, M. M. and Browne, J. S. L.: J. Clin. Endocrinol., 8: 591, 1948.

[3] Sprague, R. G.: Am. J. Med., 10: 567, 1951.

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Various pancreatic lesions, such as necrosis, cysts, or pancreatitis, as well as hepatic changes have been observed in a few of our patients with Cushing's syndrome at autopsy, but most of these patients had previous adrenal surgery, making the findings difficult to evaluate. The catabolic action of the excess 11-oxysteroids causes a variety of pathologic and metabolic changes[3] described in the section on diagnosis.

DIAGNOSIS

The classical case of Cushing's syndrome is easy to recognize. The most striking feature is the facial appearance, consisting of a plethoric, round "moon face." Women often have hirsutism with various degrees of beard formation, particularly in cases where there are manifestations of the adrenogenital syndrome. The neck is short and obese, and there is usually a "buffalo" hump of fat in the cervicodorsal region. The abdomen protrudes because of obesity and weakness of the abdominal musculature. The limbs appear wasted with weak, flabby muscles which have decreased in size as the syndrome progresses. This muscular weakness is often a striking feature of the syndrome. The skin is thin and the blood vessels are more evident than in normal people. There are usually purplish striae over the upper thighs and lower abdomen. Easy bruisability of the skin is common and acne is sometimes present, as well as other minor skin infections.

Various degrees of arterial hypertension are found, usually of a labile nature. If hypertension has been present for a long period, it may not decrease in spite of adequate surgical therapy. Associated with the hypertension, there may be cardiac hypertrophy and some degree of cardiac failure. Diabetes mellitus is almost invariably present and insulin-resistant in type. Most women have amenorrhea or menstrual irregularity and men show decreased libido and potency. Roentgenograms of the vertebra and skull may demonstrate various degrees of osteoporosis; pathologic fractures may be found usually in the form of compression of one or more of the vertebral bodies. Back pain is common among these patients and it is believed to be associated with the osteoporotic changes in the spine. The posterior clinoid processes of the pituitary fossa may disappear because of the osteoporosis. This can be mistakenly interpreted to indicate the presence of a pituitary tumor. Lymphopenia and eosinopenia occur with hemoglobin and red cell counts increased above the range of normal, 15 to 17 gm./100 cc of hemoglobin and 5 to 7 million red cells/cu. mm. are common. This must be distinguished from polycythemia vera which is not connected with the disease. In some patients with Cushing's syndrome considerable alteration of the blood chemistry occurs, such as low serum potassium, elevation of the serum sodium and a low chloride type of alkalosis. These chemical changes are

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[20] Golden, A., Bondy, P. K. and Sheldon, W. H.: Proc. Soc. Exper. Biol. & Med., 74: 455, 1950.

[21] Laqueur, G. L.: Science, 112: 429, 1950.

of the hypothalamic centers are capable of altering the normal pituitary-adrenocortical response to stress. Controversy exists as to the mechanism involved, although the balance of evidence at present favors a humoral hypothalamic-pituitary control rather than a neural one. Much evidence may come from further investigation of serum ACTH levels in patients with Cushing's syndrome.[16] Adequate subtotal adrenal resection or removal of a functioning cortical tumor usually causes remission of the syndrome, indicating that the disturbance is probably primary in the adrenal glands.

The cause of hyperadrenocorticism in the majority of patients with Cushing's syndrome is bilateral adrenal hyperplasia with no clinical or autopsy evidence of pituitary tumor. Of 22 patients with Cushing's syndrome in our series who were operated upon or later autopsied, sixteen were found to have bilateral adrenal hyperplasia. This is recognized grossly by enlargement, nodularity, and rounding of the ordinarily sharp edges of the adrenals; however, these gross changes do not occur uniformly when hyperfunction is manifested clinically. There is a considerable variation in size and weight of the adrenal glands among normal humans, and there may be a difference in the size and weight of the adrenals in the same person. This is also true in patients with hyperadrenocorticism, and therefore, comparisons of size and weight have little practical value. Microscopically it is exceedingly difficult to distinguish a hyperfunctioning adrenal from the normal. There is usually hyperplasia of the pigmented zone of the cortex and fucsinophilic staining reaction of the cortical cells seems to be more pronounced in the adrenals of patients who show clinical evidence of cortical hyperfunction.

In five instances, or about one fourth of our patients with Cushing's syndrome, either a cortical adenoma or carcinoma of one adrenal was found. The size of the tumor is not directly related to its functional ability and a small adenoma is just as capable of producing the syndrome as a large tumor. It should be mentioned that many cortical adenomas and carcinomas have no distinguishable endocrine function.

The pituitary basophil cells undergo changes[17] consisting mainly of cytoplasmic hyalinization, loss of basophilic granules, and excessive vacuolization. Much less frequently small or microscopic basophil adenomas of the pituitary are found in association with bilateral adrenal hyperplasia.[1, 18] That some pituitary adenomas may cause the syndrome appears to be demonstrated by the occasional striking clinical remission which follows pituitary irradiation. On the other hand, pituitary adenomas are found frequently at autopsy in patients who had no endocrine abnormality clinically. Crooke's changes of the basophil cells occur far more often than pituitary adenoma in patients with hyperadrenocorticism. In comparison, patients with Addison's disease often have a paucity of basophil cells in the pituitary.[19] Changes in the basophil cells can be caused the central vein and containing at least one arterial branch. All of the opposite gland is removed. It has been customary to remove the second gland at a later date, usually about 2 weeks after bilateral exploration. Now that satisfactory replacement therapy is available, both procedures can be done in one operation without undue risk. It is difficult to estimate how much adrenal tissue should be excised. It is believed that enough should be removed to cause temporary relative adrenal cortical insufficiency from which the patient gradually recovers with remission of the syndrome. This means that 85 to 90 per cent of all adrenal tissue should be removed. To insure viability of the remaining portion great care must be exercised in hemostasis and preservation of the central vein and the arterial supply along the medial edge of the gland.

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[16] Taylor, A. B., Albert, A. and Sprague, R. G.: Endocrinology, 45: 335, 1949.

[17] Crooke, A. C.: J. Path. & Bact., 41: 339, 1935.

[18] Kepler, E. J. and Locke, W.: Textbook of Endocrinology. Edited by R. H. Williams. Philadelphia: W. B. Saunders Co., 1950, pp. 180-248.

[19] Krause, E. J.: Virchow's Arch. Path. Anat., 247: 421, 1923.

At present we do not believe that it is justifiable to remove all of both adrenal glands for Cushing's syndrome unless it is apparent that the disease is progressive following subtotal adrenalectomy as outlined and a serious threat to life. The possibility of aberrantly located adrenal cortical tissue must be kept in mind if symptoms and signs progress postoperatively.

PREOPERATIVE AND POSTOPERATIVE HORMONE MANAGEMENT

Cortisone, ACTH and desoxycorticosterone have simplified the treatment of patients with Cushing's syndrome. There is often no way of establishing prior to exploration whether an adrenal tumor or bilateral hyperplasia is the cause of the syndrome; therefore all patients should be prepared with cortisone 24 hours before operation. This is given in doses of 25 to 100 mg. intramuscularly or orally every 6 hours, the last dose being administered about 2 hours prior to the operation. This insures an adequate supply of cortisone in the event that an adrenal tumor is found with atrophy of the opposite gland. Cortisone should be continued for a few days after operation and is gradually withdrawn within the first week. Should nausea, vomiting, fever, or weakness develop, cortisone is resumed in small doses. The administration of ACTH in doses of 25 mg. intramuscularly every 8 hours facilitates recovery of an atrophic adrenal gland.

If bilateral adrenal hyperplasia is found and subtotal resection of one adrenal performed as a first stage procedure, cortisone is not necessary postoperatively. When total removal of the remaining adrenal is done or if both procedures are performed in one operation, cortisone must be given until the patient shows a satisfactory recovery. It is withdrawn gradually and the patient carefully observed for signs or symptoms of adrenocortical insufficiency. These are nausea, vomiting, weakness, muscle pains or stiffness, unexplained fever, and hypotension. Treatment should always be instituted before the symptoms and signs of acute adrenal failure of the Waterhouse-Friderichsen syndrome are manifested. The symptoms can be controlled by small amounts of cortisone orally. In some instances, cortisone may have to be given continuously because of failure of the remaining fragment of adrenal gland to supply sufficient adrenocorticoids. The adrenalin and ACTH test should not be relied upon postoperatively as a measure of adrenocortical function and therapy must depend upon the clinical response of the patient. Blood chemistry studies must be carefully followed postoperadue to the increased excretion of potassium by the kidney with retention of sodium and water in the system. Pyelonephritis and even renal calculi occur frequently, particularly when hypercalcinuria exists. The average 17-ketosteroid excretion of a large group of patients with adrenal hyperplasia was 18.1, with benign tumor 5.7, and with malignant tumor 124.4 mg./24 hours.[11] Urinary corticoid levels by present chemical tests are not usually diagnostic.

A number of women with Cushing's syndrome show manifestations of the adrenogenital syndrome as well, presenting all gradations of masculinity. These women are healthy and do not become weak. They have the characteristic obesity and round plethoric face but with increased hirsutism and some degree of baldness. Amenorrhea may be a symptom and clitoral enlargement is often found.

In every case of Cushing's syndrome the question arises regarding the possible presence of a basophilic pituitary tumor. Roentgenograms of the skull almost invariably show a normal sella turcica. Should widening of the sella occur, it is logical to assume that a basophilic tumor is present but such instances are rare. A report appeared recently of co-existing Cushing's syndrome and acromegaly in association with an acidophilic pituitary tumor.[22]

TREATMENT

All patients with Cushing's syndrome should have careful roentgenographic examination of the adrenal areas. Excretory urography may disclose downward displacement of a kidney indicating the presence of a suprarenal tumor. This can be confirmed by translumbar aortography, posterior laminograms, or, as done in some clinics, perirenal air insufflation. Preoperative localization of an adrenal tumor greatly simplifies the surgical problem, for the tumor can be removed by way of the thoraco-abdominal or flank approach without the necessity of exploring both adrenals. Usually no tumor is localized preoperatively and we believe simultaneous bilateral exploration should be performed, for it is important to establish the pathologic lesion in both adrenals before any definitive procedure is carried out. By utilizing bilateral posterovertical incisions[23] adequate simultaneous exposure of both adrenals is possible. Many prefer to use the classical flank or posterolateral approach as for a nephrectomy, but this limits exploration to one side at a time. Small benign, but hyperfunctioning adrenal tumors which cause atrophy of the opposite adrenal gland can seldom be localized preoperatively. Adenomas can be enucleated readily from the adrenal gland; however, should doubt exist as to the nature of the growth the entire gland should be removed. If both adrenals appear atrophic a search must be made for an aberrantly located adrenal adenoma.

When both glands are found to be nodular and enlarged with rounded edges the pathologic entity is adrenal hyperplasia. The two glands may not be the same size or have the same weight. According to the present concept of therapy at least four-fifths of one adrenal gland is excised, sparing the portion around

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[22] McCormick, R. V., Reed, C. E., Murray, R. H. and Ray, B. S.: Am. J. Med., 10: 662, 1951.

[23] Young, H. H.: Surg. Gynec. & Obst., 63: 179, 1936.

On examination she had a normal temperature, pulse and respiration. Her blood pressure was 195/115. She had a rounded, plethoric face; there was excess of fine hair over the face and coarse hair on the arms, legs, and breasts (fig. 1). She was obese with heavy fat deposits over the trunk, shoulders and hips. Broad silvery striae were present over the lower trunk and thighs. Old acne scars were evident over the back and the skin was of coarse texture. The pupils were normal and examination of the fundi showed normal optic disks. There was slight constriction of the retinal vessels but no hemorrhages or exudate. Examination of the ears, nose and throat revealed no abnormalities. The lymph nodes were normal. The breasts were large and pendulous. The lungs were clear to auscultation and percussion. The heart was not enlarged and the sounds were normal. The abdomen was obese but there were no palpably enlarged organs or masses or areas of tenderness. The external genitalia were normally feminine. The cervix was normal to inspection and the uterus and adnexae were normal to palpation. Neurologic examination was completely normal.

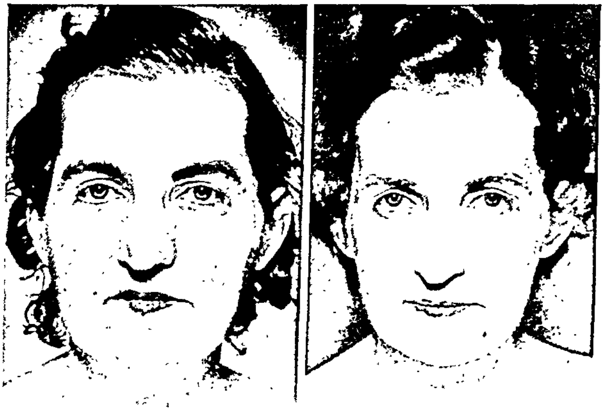

FIG. 1. Patient with Cushing's syndrome before and 5 months after subtotal adrenalectomy.

It was believed that she had adrenocortical hyperfunction, presenting features predominately of Cushing's syndrome, but also some of adrenogenital syndrome. The laboratory data were as follows: Serology negative; hemoglobin 16.4 gm./100 cc; red blood count 6,250,000/cu. mm.; white blood count 8700; fasting blood sugar 173 mg./100 cc; blood urea 33 mg./100 cc; plasma CO_2 56 vol. per cent; plasma chlorides 577 mg./100 cc; serum potassium 4.1 mEq/liter. The urine had a specific gravity of 1.017; pH 7.5; albumin negative; sugar 3 plus; no acetone; 2 to 3 white blood cell per high power field. The single dose oral glucose tolerance test was as follows: fasting blood sugar 114 mg./100 cc; half hour 184; one hour 270; two hours 333; three hours 250; four hours 197. There was a 4 plus glycosuria in all specimens collected during this test. She was placed on a diet of 100 gm. of carbohydrate, 62 gm. of protein, and 50 gm. of fat daily. On this regimen her blood sugar stabilized to around 130 mg./100 cc. On one occasion when she had a "black out" spell her blood sugar was 82 mg./100 cc.

tively particularly the serum sodium and potassium levels, as serious alteration may develop. Hypoglycemia may also occur postoperatively. There is sufficient desoxycorticosterone-like material in cortisone to supply the daily need of this hormone in most patients. It may be necessary to use DCA in doses of 1 to 3 mg. daily in those patients in whom hypotension or low serum sodium levels are not well controlled by oral sodium chloride in doses of 4 to 6 gm. daily as enteric coated tablets.

RESULTS OF SURGERY

It is important to understand that Cushing's syndrome is a progressive disease which greatly shortens life expectancy. It is also important to realize that the clinical picture is caused either by an adrenal tumor or bilateral adrenal hyperplasia in practically all instances. Surgical removal of functioning adrenocortical tumors usually results in remission of the syndrome. Subtotal adrenalectomy for bilateral hyperplasia also results in remission of the syndrome provided sufficient adrenocortical tissue has been excised.[24] If there is no regression of Cushing's syndrome postoperatively, too much functioning cortical tissue remains. Return of the syndrome following temporary remission is an indication for removal of more adrenal tissue. Until more is known regarding adrenocortical function and better methods are developed for handling hyperfunction, subtotal adrenalectomy will be the procedure of choice for bilateral adrenal hyperplasia. The problems associated with the diagnosis, surgical handling and postoperative care of patients with Cushing's syndrome are illustrated by the following case report:

A 34 year old white housewife was first seen March 15, 1951 with a chief complaint of "blacking out" spells of several years' duration. These spells occurred every few months and lasted for 5 to 10 minutes during which time she seemed to be asleep, acted automatically, and was disoriented and unable to talk. There was no relation of the spells to food intake. In the 4 months prior to entry the spells increased in frequency, occurring 2 or 3 times weekly. There were also 3 major spells characterized by sudden onset of severe back pain, sweating, weakness, palpitation, stupor, and generalized convulsions lasting for several minutes.

She was found to have diabetes 2 years before. This was treated by diet and the daily use of 6 to 10 units of PZI. There had been no known insulin reactions during this period. She had lost 15 pounds of weight in the 3 months prior to entry, but was still much overweight, weighing 197 pounds. Her height was 5 feet and 3 inches. Hypertension was discovered by her physician shortly prior to entry. Her periods had always been irregular and she had not menstruated for 7 years, although her youngest child was only 5 years of age. Her other child was 12 years of age. She had moderate exertional dyspnea and palpitation, but experienced no other cardiovascular symptoms. Urinary frequency, burning and nocturia had been present for 4 months. There was no family history of hypertension; however her mother was said to have died of diabetes and heart disease.

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[24] Priestley, J. T., Sprague, R. G., Walters, W. and Salassa, R. M.: Ann. Surg., 134: 464, 1951.

apparently occasionally initiated by a pituitary basophilic tumor, resulting in adrenal hyperplasia and hyperfunction. The classical Cushing's syndrome is due to a hypersecretion of 11-oxysteroids. Many patients show mixed adrenogenital and Cushing's syndrome probably due to an excess of androsterone and related compounds as well as the 11-oxysteroids. The syndrome can be induced artificially by ACTH, cortisone, or compound F.

When surgical treatment is recommended, simultaneous bilateral adrenal exploration should be done to determine the underlying pathologic process before any definitive surgical procedure is carried out. Removal of a functioning adrenocortical tumor results in disappearance of the syndrome. Cushing's syndrome due to bilateral adrenal hyperplasia can be treated effectively by adequate subtotal removal of one adrenal and total removal of the other gland, cortisone being used as indicated during the postoperative phase. When a basophilic pituitary tumor is suspected, roentgen therapy can be tried. The proper use of cortisone alone or in conjunction with ACTH has decreased the hazards of surgery greatly.

normal limits. She had no fever or tachycardia, and her nausea gradually disappeared. Her fasting blood sugar level without insulin ranged between 140 and 216 mg./100 cc postoperatively. Glycosuria persisted up to the time of her discharge from the hospital 16 days following the second operation. ACTH test prior to discharge showed a 40 per cent drop in circulating eosinophils at the end of 4 hours.

She was advised to take enteric-coated salt tablets, 4 gm. daily and 2 mg. of desoxycorticosterone twice daily. Approximately one month after discharge, she began to develop spells of nausea, vomiting and abdominal distress with recurrent bouts of upper respiratory infections. Three months following operation, she was started on cortisone, 12.5 mg., 4 times daily and felt greatly improved. All symptoms of nausea, vomiting, fever and weakness disappeared with this therapy. However, on withdrawal of this drug, her symptoms promptly returned.

She was re-admitted to the hospital on August 27, 1951. She had lost 75 pounds in weight. The hair had disappeared from her face and body and was falling out of her forearms and legs. She had sustained no seizures postoperatively. There had been a noticeable improvement in the facial appearance with loss of the fat over the face, trunk and upper dorsal areas. There was no abnormal pigmentation of the skin or buccal mucous membranes. She experienced muscular weakness, especially of the thighs, calves and forearms. The serum sodium was 131 mEq/liter, serum potassium 4.5 mEq/liter. Her blood hemoglobin was 8.5/gm. per 100 cc; white count 5,800; red cell count 3,530,000. The blood urea was 33 mg./100 cc; blood chlorides were 561 mg./100 cc; Kepler index was 5. Fasting direct eosinophil count was 69 per cu. mm. and there was no drop in eosinophils 4 hours after 25 mg. of ACTH.

While undergoing an oral glucose tolerance test, the patient had a typical Addisonian collapse, which responded promptly to intravenous glucose and saline with added adrenocortical extract. Cortisone, 12.5 mg., 4 times daily, was re-instituted with added salt, 2 gm., 3 times a day. Improvement in strength was rapid with increase in her appetite and she was discharged on this medication. One month later she was in good health with no recurrence of nausea or vomiting. Her weight was 150 pounds, her pulse 78, blood pressure 160/90. There was some edema of both ankles. For the first time in 7 years she had menstruated. There was no glycosuria at this time.

After another month she was symptom free, doing all her ordinary housework. She had now had two menstrual periods at intervals of 4 weeks, the first two in 7 years. Hair had continued to disappear from the extremities. Her weight was 152 pounds and her blood pressure 136/90. Kepler water excretion test was still abnormal showing an index of 12. Blood potassium was 4.5 mEq/liter.

SUMMARY

Cushing's syndrome results from hyperfunction of the adrenal cortex. The pathologic process causing the endocrine disorder is bilateral adrenal hyperplasia or a unilateral tumor, in a ratio of about three to one. The syndrome is urine was to be infected with Salmonella enteritidis and a subgroup of control animals. Two operations, separated by an interval of 6 weeks, were performed on all animals.

At the first operation, using aseptic technique, a foreign body was introduced into the bladder through a suprapubic cystotomy. The foreign body in each instance consisted of a flat rectangular piece of zinc weighing approximately 10 mg. In the subgroups to be infected, the organism was introduced by washing the foreign body in a Brewer's broth culture of Salmonella enteritidis immediately prior to its insertion in the bladder. To make strict comparison possible, the foreign body to be inserted in each control rat was previously washed in sterile Brewer's broth medium. The bladder was closed with a fine silk suture and the abdominal incision repaired.

A stock diet of Purina Fox Chow Checkers and drinking water were available to the animals at all times. Normal rats on this diet do not form calculi spontaneously. However, as we have already shown, if a zinc foreign body be present, a magnesium ammonium phosphate calculus is rapidly produced around it.

Six weeks after the initial operation the second operation was performed. The bladder was again exposed, and its urine aspirated with a sterile syringe and needle. After opening the bladder, the stones were removed and weighed upon an analytical balance. In some instances where large stones had developed, small "daughter" stones were also found associated with them. These "daughter" stones have not been included in the stone weights recorded in the accompanying tables. Whenever a sufficient volume of urine was aspirated, its pH was determined with a Beckman pH meter. Cultures of the urine were then made on blood agar plates and in Brewer's anaerobic media.

The bacterial cultures were examined 48 hours after inoculation. In the infected group, Salmonella enteritidis was recovered in pure culture from the urine of all surviving rats. If the urine of any of the control animals was found to have become accidentally infected, such animals were excluded from the series. Strict comparison could therefore be made between stone growth in animals whose urine was infected with Salmonella enteritidis and controls whose urine had remained sterile throughout the experiment.

A quantitative study was made of the urinary excretion of magnesium, calcium, phosphorus, and ammonia nitrogen in order to determine if Salmonella infection inhibits stone formation by altering the concentration of any of these substances. Four weeks from the original operation urine was collected for 3 consecutive days from 8 rats of the sterile group and from an equal number of the infected group and the appropriate determinations made. The ammonia nitrogen was estimated by a photometric modification of Folin and Bell's method.[5] The methods for the other chemical determinations are described in previous papers.

Results. The degree of stone formation in the sterile controls was in marked contrast to that found in the infected animals. In the controls the incidence and average weight of stone was found to correspond with the results obtained in

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[5] Levinson, S. A. and MacFate, R. P.: Clinical Laboratory Diagnosis. Philadelphia: Lea and Febiger, 1943, p. 426.

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EXPERIMENTAL UROLITHIASIS

V. PREVENTION AND DISSOLUTION OF FOREIGN BODY CALCULI BY INFECTION WITH SALMONELLA ENTERITIDIS

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In previous papers of this series on experimental urolithiasis a method has been presented for studying the process of stone formation as it occurs after introduction of a foreign body into the urinary bladder of the rat.[1, 2, 3, 4] We have as yet reported no experiments investigating the influence of infection upon stone formation although we had noted, as was to be expected, that accidental infection with a urea-splitting organism tended to augment the process. In one of our experiments, however, a chance finding led us to suspect that infection may at times exert a pronounced inhibitory effect on stone formation. This observation was first made in a group of control rats from an unrelated experiment. The group was composed of 16 animals each with a foreign body in the bladder. When the experiment was completed, 6 weeks after the foreign bodies had been implanted, it was found that an accidental infection had developed in 5 of the animals. All of these infected rats failed to produce stones while the remaining animals, whose urines were sterile, developed the expected amount of stone upon the foreign bodies. The infecting organism was identified as Salmonella Enteritidis.

The purpose of the present paper is to present further data showing that this organism has a pronounced inhibitory effect on stone formation. The experiments were of two types, the first being concerned with prevention of stone formation and the second with the dissolution of previously formed stones. Prevention was investigated by introducing Salmonella enteritidis at the time the foreign body was implanted. Dissolution was attempted by introducing the infection only after the stone had first been allowed to form in sterile urine.

EXPERIMENT I—(PREVENTION)

Methods. Four successive groups of rats were employed in this experiment, using male animals of a single strain and weighing approximately 200 gm. Each group was treated in identical fashion, being divided into a subgroup whose

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Our thanks are due to Dr. Welton I. Taylor of the Bacteriology Department, University of Illinois, for his valuable advice and assistance in the identification of the organism used in this study.

[1] Vermeulen, C. W., Grove, William J., Goetz, R., Ragins, H. D. and Correll, N. O.: J. Urol., 64: 541, 1950.

[2] Grove, William J., Vermeulen, C. W., Goetz, R. and Ragins, H. D.: J. Urol., 64: 549, 1950.

[3] Vermeulen, C. W., Ragins, H. D., Grove, William J. and Goetz, R.: J. Urol., 65: 1, 1951.

[4] Vermeulen, C. W., Goetz, R., Ragins, H. D. and Grove, William J.: J. Urol., 66: 6, 1951.

We wondered if the inhibitory effect of Salmonella infection would persist for periods longer than 6 weeks. Accordingly, at the time of the second operation, the bare zinc foreign bodies from six of the infected rats were replaced in their bladders. These six animals were then allowed to live for an additional nine weeks and at the end of this time the Salmonella enteritidis was again recovered. In no instance had stone formation occurred.

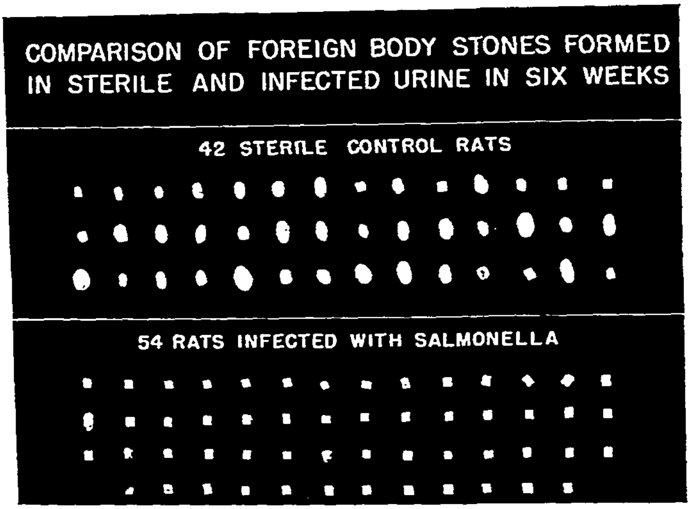
COMPARISON OF FOREIGN BODY STONES FORMED IN STERILE AND INFECTED URINE IN SIX WEEKS
42 STERILE CONTROL RATS
54 RATS INFECTED WITH SALMONELLA

FIG. 1. (Experiment 1) Photograph of bladder contents of control and Salmonella infected rats. It is seen that in sterile control rats foreign bodies are encased in stone while in infected rats foreign bodies are almost completely free of calculous deposit.

TABLE 2. *Average values on analysis of urine*

	URINE COLLECTED 3 DAYS FROM 8 RATS IN EACH GROUP					pH AT OPERATION
	Volume	Calcium	Magnesium	Phosphorus	Ammonia N_2	
	cc., diem	*mg. %*	*mg. %*	*mg. %*	*mg. %*	
Sterile control	15.8	21.2	33.6	125	43	6.7 (34 rats)
Salmonella infected	20.1	17.7	29.1	105	44	6.72 (45 rats)

EXPERIMENT II—(DISSOLUTION)

Methods. Having established that Salmonella enteritidis is capable of preventing foreign body stone formation, an experiment was now designed to study the effect of delaying such infection until stones had already formed. Rats were again used, and at the first operation a standard zinc foreign body was introduced into the bladder by the usual aseptic technique. Six weeks later the bladders were reopened after aspiration of the urine for culture. In the instances where stones had formed they were removed, weighed and re-implanted. In one half of the rats the stones, prior to their re-implantation, were washed in a Brewer's broth culture of Salmonella enteritidis. In the remaining animals which were to serve as controls, the stones were simply washed in sterile Brewer's broth before re-implantation. It will be noted that in the group to be infected previous experiments. On the other hand, the absence of stone formation in the infected animals was most striking. The results obtained from the four experimental groups are shown in table 1. If the figures for all four groups be combined, it is seen that stones formed in 37 of 42 rats with sterile urine but in only 2 of 54 rats whose urine was infected with Salmonella enteritidis. The average weight of calculus deposit in the control animals was 52.9 milligrams but only 1.8 milligrams in the infected animals. The photograph (fig. 1) clearly demonstrates this difference. Statistical analysis of these results shows that the possibility of their occurrence by chance alone is much less than 1 in 100 in the first three groups and less than 5 in 100 in the fourth group.

TABLE 1. *Prevention of calculi by Salmonella infection*

EXPERIMENTAL GROUPS		NUMBER OF RATS	RATS WITH CALCULUS WT. OVER 10 MG.	AVER. WEIGHT OF CALCULUS FOR WHOLE GROUP
				mgm.
1	Control	7	7	34.3
	Salmonella	5	0	1.0
2	Control	15	11	34.3
	Salmonella	15	1	3.5
3	Control	15	15	84.6
	Salmonella	28	1	0.9
4	Control	5	4	39.4
	Salmonella	6	0	0.0
ALL GROUPS COMBINED				
	Control	42	37	52.9 ± 7.4 (S.E.)
	Salmonella	54	2	1.8 ± 0.82

Statistical comparison all groups combined:
Stone weight, control vs. Salmonella — t = 7.813.

In table 2 the average daily volume and chemical composition of urine from the control and infected rats are compared. It was found that the urine volume was somewhat greater in the infected rats and was accompanied by a corresponding dilution of calcium, magnesium, and phosphorus, while the ammonia nitrogen remained unchanged. We do not believe that these chemical findings explain the failure of calculus formation in the presence of Salmonella infection. The infection also failed to produce any significant change in the urinary pH as judged by the values obtained at the end of the experiment. The average for the controls was 6.70 while that for the infected rats was 6.72. It should be emphasized that the Salmonella infection appeared to remain limited to the urinary tract. No systemic disturbance was apparent. Representative histological sections of the bladder wall of a control and an infected animal are shown in the photomicrographs (fig. 2). In both sections the mucosa is intact and of normal thickness, with a few chronic inflammatory cells in the submucosa.

most cases continued to grow. In the other group the stones decreased in size after the Salmonella infection was introduced. In the 11 animals of the control group, one stone lost weight, 3 stones remained essentially unchanged, while in the remaining 7 animals the stones continued to grow. For the entire group of controls the stones showed an average increase in weight of 50 mg. On the other hand, after the infection was introduced into the bladder of the 12 animals of the second group, only one stone gained weight, another remained unchanged, while the remaining 10 all lost weight significantly. Dissolution of stone was complete in 4 instances leaving the zinc foreign body bare in the bladder. For the entire group of rats infected with Salmonella, the stones showed an average weight loss of 58 mg., which is in sharp contrast to the average gain of 50 mg. in the controls.

TABLE 3. *Dissolution of calculi by Salmonella infection*

NO. OF RATS	AV. INITIAL STONE WT.	PROCEDURE AT REIMPLANTATION	AV. STONE WT. 4 WKS. LATER	AV. CHANGE IN WT. OF STONE
	mg.		mg.	mg.
11	42	No infection introduced	92	+50
12	108	Salmonella introduced	50	−58

Statistical comparison—change in weight of stone:

$t = 4.734$

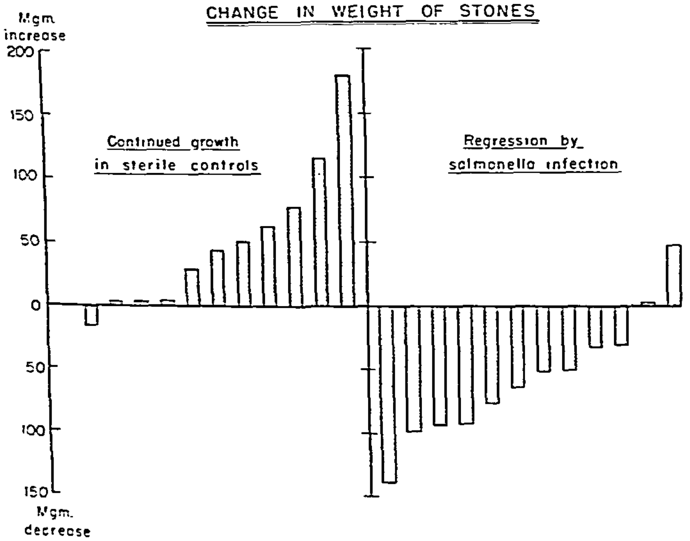

FIG. 3. (Experiment 2—Dissolution). Graph showing changes in weights of individual stones in 2 series of rats in last 4 weeks of experiment. Gain or loss in weight of stone is indicated for each rat by length of bar above or below zero base line.

DISCUSSION

Infection is ordinarily considered to be an important factor in the formation and growth of urinary calculi. The evidence for such a relationship seems to be with Salmonella, the stones were considerably larger than in those whose urine was to remain sterile. This provided a severe test of the "dissolving power" of the infection in rats whose stones had been rapidly growing up to the time when the infection was introduced.

Four weeks after the second operation the bladder was again exposed. The urine was aspirated for culture and the stone removed and weighed. The change which occurred in the weight of the stones during the four weeks of Salmonella infection could then be compared with that occurring in the control animals. It should be stated that only such animals are included in the control group whose urine was proved to be sterile throughout the experiment. Likewise, the Salmonella group includes only those animals which yielded a sterile urine immediately prior to the introduction of the Salmonella and from which, at the end of the experiment, Salmonella was recovered in pure culture.

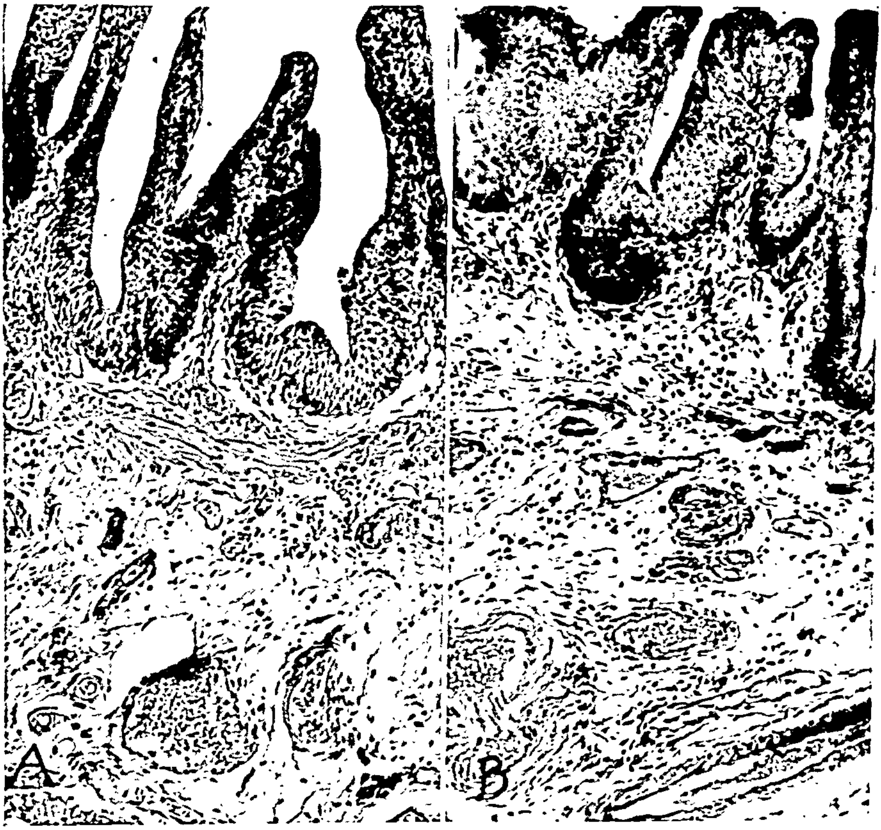

FIG. 2. *A*, photomicrograph (× 132) of bladder of rat with sterile urine. *B*, photomicrograph (× 132) of bladder of rat with Salmonella infection.

Results. The results indicate that Salmonella enteritidis, already shown to be capable of inhibiting stone formation, is further able to effect a reversal of the process if the introduction of the infection is delayed until stones have already formed. As can be seen in table 3 and figure 3, the stones in the control group in

SUMMARY

In a continuing study of stone formation as it occurs on foreign bodies in the bladders of rats, it was found that infection with Salmonella enteritidis is able to prevent stones that would otherwise occur on the foreign bodies. An additional experiment demonstrated that if the infection is introduced only after stones have already formed, the infection is capable of producing regression and sometimes complete dissolution of such stones. The mechanism by which the infection produces stone inhibition is as yet unknown. No change was detected in either the urinary pH or the urinary excretion of the crystalloid components of the stone.

quite satisfactory when the infection is of the urea-splitting variety. The increased alkalinity of the urine along with the increased concentration of urinary ammonia satisfactorily explains the rapid development of stones in the presence of this type of infection. Animal experiments have also confirmed the clinical impression that infection with urea-splitting organisms augments stone formation.[6, 7]

The possibility that infection could ever inhibit stone formation does not seem to have been seriously considered. The data presented here indicate to us that under the experimental conditions used, such a possibility does indeed exist. It is true that an occasional stone developed in the first experiment despite the presence of Salmonella infection but when the infected animals as a group are compared with the uninfected controls a striking difference is evident. This conclusion is strengthened by the results of the second experiment where Salmonella infection was found to be capable of dissolving stones that had previously been formed in sterile urine. It is our belief that the infection does not act by altering the surface characteristics of the foreign body. It would be difficult to believe that dissolution of calculi would occur if this were so, for the foreign body in the dissolution experiments was completely encased in the stone. Apparently the infection acts not on the foreign body but on the stone itself, either its crystalline or matrix component.

At the present time an explanation of the action of Salmonella infection is not available. It is evident that the infection does not act by producing acidification of the urine, for no difference in the urinary pH could be detected. Likewise chemical study of the urine has failed to show any significant change in the concentrations of the ionic components of the stone. Histologic study of the bladders of the infected rats has not shown any great change in the mucosa; actually, remarkably little local or general inflammatory reaction was found.

One might speculate that Salmonella infection acts upon the crystalline component of the stone despite the negative evidence already mentioned. It may be that a chemical agent is produced, or some urinary colloidal change occurs that leads to an increase in solubility of the crystalloid. It might even be postulated that the growing organisms act as colloidal particles which bind to themselves the crystalline material that would otherwise lead to the formation of a stone. Then again, it is conceivable that Salmonella growing in the urine produces an enzyme which destroys or in some way alters the material composing the stone matrix or binding substance so that a stone cannot be formed. Experiments in vitro have so far failed completely when attempts were made to dissolve stones in urine infected with Salmonella.

We do not wish to suggest in this paper that our findings have any immediate clinical application; but a knowledge of the mechanism by which Salmonella infection prevents and dissolves stones might well throw further light on the problem of urolithiasis. Other experiments are therefore in progress using this and other similar organisms.

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[6] Hager, B. H. and Magath, T. B.: J. A. M. A., 85: 1352, 1925.
[7] Davalos, H. A., Jr.: J. Urol., 49: 639, 1943.

with the natural history of pyelonephritis, as delineated by Longcope and Winkenwerder,[6] and to be totally unlike the natural history of any other form of Bright's disease. Thus, from our point of view, pyelonephritis is indeed an important disease.

Another reason for our interest in pyelonephritis is that it seems to us to be, in general, a poorly managed disease. This rather dogmatic statement is made for two reasons:

First, if we let figure 1 represent the life span of a patient with typical pyelonephritis, it is evident that there has been no continuity in treatment. The chills and fever which first appeared in childhood were, of course, treated by a pediatrician. The patient was then relatively free of symptoms until she married at the age of 18 years, when the so-typical "honeymoon pyelitis" developed. She consulted a gynecologist, who probably forced fluids and administered small doses of sulfonamides and, again, she apparently recovered. Shortly afterward she became pregnant and once again symptoms of pyelonephritis, with or without toxemia of pregnancy,[7, 8] developed. At that time, of course, she was treated by her obstetrician. Finally, at about the age of 30 years the chills, fever, back pain and dysuria returned. Since symptoms were referable to the urinary tract, she consulted a urologist, who made the necessary examinations and treated her with mandelic acid, or possibly 0.5 gm. of gantrisin 4 times a day. Under this regimen the acute episode subsided, and she never again complained of chills, fever or even dysuria. However, she soon began to tire easily, looked pale, and had to force herself to complete her routine daily chores. Finally, she returned to the urologist, who discovered that she was anemic, the blood urea nitrogen was elevated, phenolsulfonphthalein excretion was depressed, erythrocyte sedi-

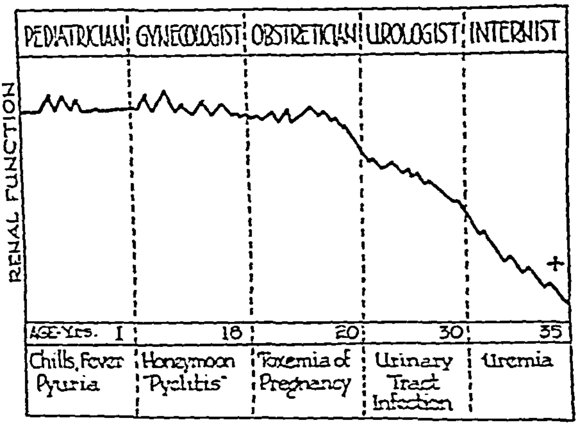

FIG. 1. Schematic representation of natural history of pyelonephritis

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[6] Longcope, W. T. and Winkenwerder, W. L.: Bull. Johns Hopkins Hosp., 53: 255-287, 1933.

[7] Peters, J. P.: New Eng. J. Med., 213: 653-659, 1935.

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THE RESPONSIBILITY OF AN INTERNIST IN THE TREATMENT OF PYELONEPHRITIS

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The privilege of addressing the members of another specialty on a subject which is one of their problems is stimulating. True, it imposes certain limitations, for it would obviously be fruitless to discuss the pathology of pyelonephritis or the differential diagnosis of its various phases, or even the indications for use of the various antibiotics. These are accepted as the urologist's domain, and he should be completely familiar with them. However, it does offer the opportunity of discussing the reasons for the difference in our therapeutic approach and yours.

First, let me explain why we internists should have a definite therapeutic approach to a disease which is most often treated by the urologist. We are, of necessity, interested in the manner in which the kidney, as a highly specialized organ, maintains a constant internal environment for every cell in the body. Therefore, we must be just as interested in the manner in which each renal disease alters the integrity of that organ and so upsets the delicately maintained equilibrium. Of all renal diseases acute pyelonephritis is the commonest,[1-4] a contention Mansfield, Mallory and Ellis[5] proved by finding the scars of healed pyelonephritis in nearly 15 per cent of 1000 consecutive autopsies. The chronic stage, as demonstrated by Weiss and Parker,[1] not only is commoner than chronic glomerulonephritis but also is responsible for the smallest kidneys of chronic Bright's disease and for 15 to 20 per cent of all examples of necrotizing arteriolitis.[2] This is further documented by the experience of every internist of having been asked to see in consultation a patient who has both hypertension and renal insufficiency. Relatives and the referring physician are anxious to know the treatment and prognosis, and, of course, both of these, depend, to a considerable extent, upon an accurate diagnosis. Physical examination helps little, since the fundi, heart and blood pressure may all be affected to varying degrees by almost any type of renal disease. Laboratory studies, with the exception of a careful examination of the urinary sediment, an excretory urogram, and a urine culture provide only a cross sectional view of renal function at the time the patient is examined, but help little in establishing the correct clinical diagnosis. We are therefore forced to rely primarily on what the patient tells us about his disease. With extraordinary frequency we find the patient's history to be compatible

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Presented before annual meeting of Clinical Society of Genito-Urinary Surgeons, New Orleans, February 7, 1952.

[1] Weiss, S. and Parker, F., Jr.: Medicine, **18:** 221–315, 1939.

[2] Weiss, S. and Parker, F., Jr.: New Eng. J. Med., **223:** 959–967, 1940.

[3] Nesbit, R. M. and Conger, K. B.: New York State J. Med., **42:** 225–232, 1942.

[4] Braasch, W. F. and Cathcart, E. P.: J. A. M. A., **88:** 1630–1633, 1927.

[5] Mansfield, J. S., Mallory, G. K. and Ellis, L. B.: New Eng. J. Med., **229:** 387–395, 1943.

times a day. Such a scheme of therapy can be expected to inhibit multiplication of organisms in the pelvis, ureter and bladder, decrease the likelihood of re-infection by sterilizing the urine and reduce the superficial inflammation of the mucosa by direct perfusion and absorption of the drug. In turn, this will alleviate the symptoms of associated or secondary cystitis and urethritis. Although

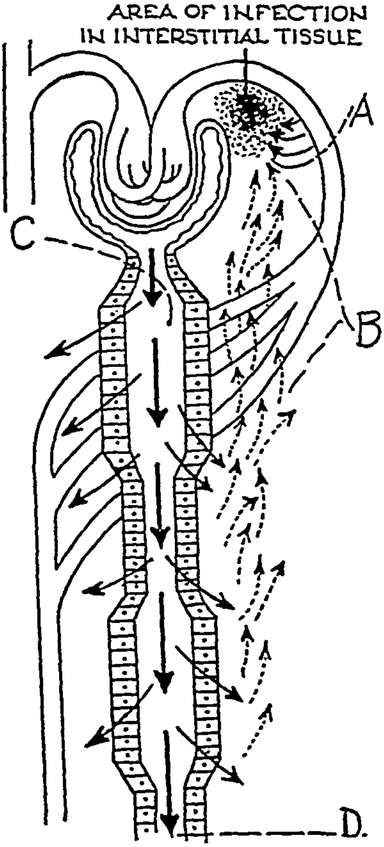

FIG. 2. Diagrammatic sketch showing calculated concentration of sulfadiazine in interstitial tissue of kidney when plasma concentration of sulfadiazine is 4 mg. %. *A*, plasma concentration of sulfadiazine = 4 mg. %. Tissue concentration of diffusable sulfadiazine = 3.4 mg. %; pH = 7.4. *B*, amount of fluid reabsorbed per minute = 119 cc. Amount of sulfadiazine reabsorbed per minute = 2.7 mg. Concentration of sulfadiazine in tubular reabsorbate = 2.4 mg. %; pH = 7.4. *C*, amount of fluid filtered per minute = 120 cc. Amount of sulfadiazine filtered per minute = 4.1 mg. Concentration of sulfadiazine in glomerular filtrate = 3.4 mg. %; pH = 7.4. *D*, amount of urine formed per minute = 1 cc. Amount of sulfadiazine excreted per minute = 1.4 mg. Concentration of sulfadiazine in urine = 140 mg. %; pH = 5.5.

this regimen is apparently successful in the majority of patients with acute pyelonephritis, the formidable number of patients in whom terminal chronic pyelonephritis ultimately develops casts considerable doubt on its actual efficacy and calls into question the wisdom of directing our efforts toward sterilization of the urine.

On the other hand, if one actually considers pyelonephritis to be an infection mentation rate was greatly elevated and an excretory urogram showed minimal concentration of the dye. She was considered to have bilateral renal disease and therefore transferred to the medical service.

This history, and it is fairly typical of pyelonephritis, suggests that the early stages of the disease are too often treated as entities by the pediatrician, obstetrician and even urologist, and not until terminal renal insufficiency appears is the internist consulted. This lack of continuity in observation and management has tended to absolve each from the responsibility of devising better means of eradicating the initial infection and so helping to prevent recurrence and chronicity.

Secondly, it seems clearly established, both from the natural history and from the pathology, that pyelonephritis is simply a bacterial infection in the interstitial tissue of the kidney. If that be true, the judicious use of antibiotics should completely eradicate the disease and terminal chronic pyelonephritis should be rare. Unfortunately, it is still a much too common cause of death.

With these as introductory remarks, the therapeutic problem posed by pyelonephritis may now be considered. If we define the disease as an infection in the interstitial tissue of the kidney which, if not eradicated or if permitted to recur repeatedly, will progressively and inexorably destroy an ever increasing area of contiguous nephrons until too few remain to maintain life, we actually arrive at the crux of the problem, that is, the difference between the therapeutic approach of the internist and the urologist. It is almost as if, to borrow from Robert Frost, "Two roads diverged in a wood and I—I took the one less traveled by." The congested road, as followed I believe by most urologists, leads directly to sterilization of the urine. In order to achieve this, the optimum dosage of any antibiotic is the one which will, by virtue of the concentrating ability of the cells of the distal convoluted tubules, provide a bacteriostatic concentration of antibiotic in the urine. It is almost possible to calculate this mathematically. To use the sulfonamides as an example, it was soon established that a urinary sulfonamide concentration of 50 to 200 mg. per 100 cc is adequate to sterilize the urine against almost all organisms.[9-15] Therefore, if a urinary output of 1000 cc in 24 hours is anticipated, and it is assumed that 100 per cent of the total amount of drug ingested is absorbed, 90 per cent is excreted in the urine, and approximately 30 per cent of this is converted to the ineffective acetylated form, it is clear that a dosage of 4 gm. a day will produce an effective urinary concentration of approximately 250 mg. per 100 cc:

$$\frac{4000 \times 1.0 \times 0.9 \times 0.7}{10} = 250 \text{ mg. per } 100 \text{ cc}$$

Since a urinary concentration of 50 mg. per cent is adequate for the majority of infections, it seemed rational to recommend a dosage of 0.5 gm. three or four

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and sensitivity studies, coupled with a consideration of the spectra covered by each antibiotic.

b) Duration of treatment should be at least 7 to 10 days.

c) Intensity of treatment should be as much antibiotic as the patient can or will tolerate.

d) Urine should be cultured after treatment has been discontinued and, if still positive, a different and more intensive regimen, with consideration of combination of antibiotics, should be devised.

The problem of treating a patient with chronic pyelonephritis is difficult. Usually a prolonged and expensive investment, in many ways it is similar to that of treating a patient with subacute bacterial endocarditis. Despite the greatly reduced renal blood flow and the prevalence of avascular scar tissue, we are faced with the problem of delivering as much antibiotic as possible to the infected area. Since the renal blood flow cannot be effectively increased, the only recourse is to increase, to the upper limits of tolerance, the concentration of antibiotic in what little blood actually reaches the infected area. Most antibiotics in extremely high dosage produce almost intolerable reactions; it is this which, in most cases, limits the duration of therapy and tests one's ability to cajole, to sedate and, if necessary, almost to force the patient to accept a treatment which soon becomes repulsive. Moreover, neither should the physician nor the patient be unduly disturbed if the first course of therapy is unsuccessful. There are always other antibiotics and other combinations of them, and perserverance together with designing and redesigning the therapeutic regimen will almost certainly succeed in overcoming the infection. Repeated short courses of intensive antibiotic therapy would appear to be more efficacious than a single prolonged course administered in doses so low that at no time is the infection in the interstitial tissue of the kidney exposed to an adequate concentration of the drug. Destroyed nephrons cannot be replaced, but hypertrophy of others and subsidence of the inflammatory reaction will probably result in some degree of permanent improvement in renal function.

In conclusion, let me say that in no other field should close cooperation between the internist and the urologist be so fruitful. Infection in itself, regardless of the organ where it lodges, is the domain of the internist. An infection which does not drain cannot be effectively treated. Evaluation of the drainage and actual construction of adequate drainage of an infected kidney, if it does not initially exist, is the domain of the urologist. It would thus seem appropriate for both specialties to combine their efforts in an attempt to eradicate at the onset this potentially fatal disease.

of the interstitial tissue of the kidney, he cannot be content with simple sterilization of the exudate that appears in the urine. Comparison with the obvious futility of treating a patient with empyema by simply sterilizing the fluid in the intrapleural space seems valid. Instead, he must "take the road less traveled by" and devise a scheme of therapy aimed at eradicating the infection in the interstitial tissue of the kidney by maintaining an effective antibiotic level at the actual site of the infection. As is illustrated in figure 2, glomerular filtrate is neither concentrated nor acidified until it reaches the distal tubular segment. Therefore, the concentration of any antibiotic in the interstitial fluid of the kidney is entirely independent of its subsequently attained concentration in the urine, and can at no time exceed its concentration in the plasma. Furthermore, it should be remembered that mandelic acid and mandelamine are effective only at a pH of 5.5 or less. Since the pH of the interstitial tissue of the kidney ranges from 7.2 to 7.4, it is clear that these two drugs have no place in the treatment of pyelonephritis, and should be reserved for those rare patients who present evidence of uncomplicated cystitis or infection of the lower urinary conduit.

Therefore, with this concept in mind, a few general principles to be applied to the treatment of acute, recurrent and chronic pyelonephritis may now be presented.

1. Acute and recurrent pyelonephritis
   - a) The appropriate sulfonamide or combination of sulfonamides is usually, but of course not always, the drug of choice. Adequate urinary output and alkalinity of the urine should be assured.
   - b) Dosage of the sulfonamides should be that which will maintain a plasma level of 8 to 10 mg. per 100 cc. The dosage of other antibiotics should be proportionate.
   - c) Duration of therapy should be arbitrarily fixed at 7 to 10 days.
   - d) Cure should be established only by the demonstration of 2 or 3 negative urinary cultures obtained after all traces of antibiotics have disappeared from the urine.

This probably seems drastic, but it must be remembered that acute pyelonephritis may be a formidable and rapidly progressing disease. Necrotizing arteriolitis secondary to pyelonephritis has been demonstrated at the autopsy of a baby 6 months old.[1] Recently, with the Department of Urology, we saw a physician's wife in whom severe renal insufficiency developed within one year of her first recognizable attack of acute pyelonephritis. Still more recently, with the Department of Urology, we observed a young girl in whom the excretory urogram was normal but urine culture yielded a positive result. She received a full course of chloramphenicol but failed to return for follow-up cultures. She was seen again just 5 months later with not only a positive urine culture but also easily demonstrable hydronephrosis and obstruction at the ureteropelvic junction. It is for such reasons that, regardless of the antibiotics selected or the dosage employed, several follow-up urinary cultures must be negative before cure can be established.

2. Chronic pyelonephritis
   - a) The antibiotic should be selected according to combined urinary culture

lung field. Pulmonary osteo-arthropathy was present. A chest roentgenogram showed marked elevation of the right diaphragm reaching to the level of the third rib anteriorly and the fifth posteriorly. A progress meal and an induced pneumoperitoneum were confirmatory. Routine laboratory studies were within normal limits and on March 31, 1950, a right thoracotomy was performed. At operation, the right kidney was situated above the liver and complicated the operative repair. The diaphragm was a relaxed, thin, translucent membrane of white fibrous tissue. Plication of the diaphragm was difficult and some of the perinephritic fat was included in the suture line with medial rotation of the kidney. A urological consultation was requested and because retrograde studies seemed inadvisable an excretory urogram was done on April 25, 1950. This examination demonstrated a high right kidney extending to the level of the ninth thoracic vertebra (fig. 1). Further surgery was deemed unnecessary.

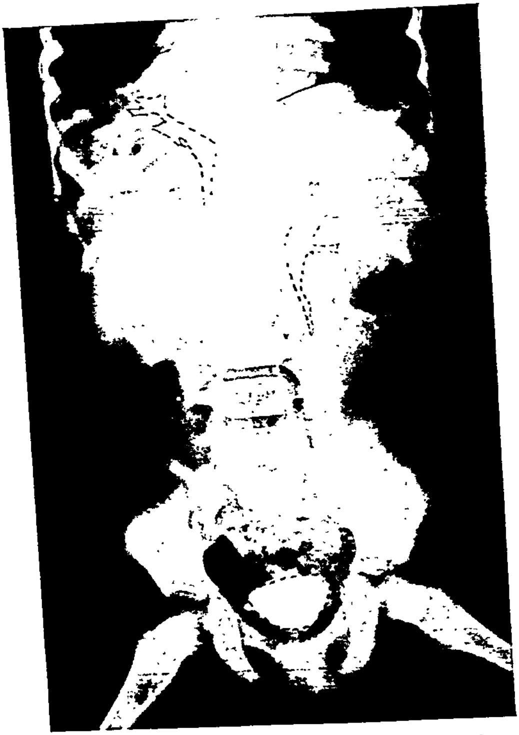

FIG. 1. Retouched postoperative excretory urogram demonstrates right kidney extending to level of ninth thoracic vertebra. Renal elements are not clearly outlined and some medial rotation is present.

COMMENT

Upward displacement of the kidney may occur with eventration of the diaphragm. The uneven time schedule and diverse origin of the several components of both kidney and diaphragm strongly suggest an embryological basis for the high kidney in diaphragmatic eventration. This hypothesis is strongly favoured

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RIGHT DIAPHRAGMATIC EVENTRATION WITH RENAL DISPLACEMENT: CASE REPORT

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Jean Louis Petit in 1790 described a condition of the diaphragm which was later termed "eventratio diaphragmatica" by Beclard. In this disorder, the intact diaphragmatic leaf is abnormally elevated and usually results from: congenital deficiency of the musculature; degenerative changes in the nerve supply with subsequent atrophy, or after deliberate operations upon the phrenic nerve. It is this weakness or insufficiency which allows one or more of the abdominal organs and rarely retroperitoneal structures to ascend within the topographical confines of the chest. Cases of disphragmatic eventration are no longer considered unusual; however, instances of eventration with associated renal involvement are decidedly uncommon and therefore warrant more detailed consideration.

A review of the available literature disclosed only two other descriptions of upward migration of the kidney in diaphragmatic eventration. Wolfroom encountered a case similar to that of the present authors in 1940, and Baurys (1949) reported displacement of the left kidney.

Upward displacement of the kidney associated with diaphragmatic eventration should be differentiated from the high renal ectopy which occasionally occurs in either congenital or traumatic diaphragmatic hernia.

In congenital hernia of the diaphragm a portion or all of the leaf is absent which allows the abdominal viscera and rarely the kidney to protrude into the thorax. The most common defect is a failure in fusion at the pleuroperitoneal hiatus or foramen of Bochdalek.

Traumatic rupture of the diaphragm may predispose to a high kidney, particularly after thoraco-abdominal injury. A true sac is generally absent in the congenital and traumatic types of diaphragmatic hernia.

It is not the purpose of this paper to present a comprehensive discussion of eventration. Briefly, roentgenograms of the chest will reveal the diaphragm in an even, curved arch extending from the costal margin to the mediastinum. On fluoroscopy, the excursions will be normal, diminished, absent or paradoxical (Kienboch phenomenon). A diagnostic pneumothorax or pneumoperitoneum will distinguish eventration from diaphragmatic hernia, because in the former the air will be retained by the intact diaphragmatic leaf.

CASE REPORT

D. P., a 4 year old Negro deaf-mute, was admitted to the thoracic service of the Boston City Hospital on March 25, 1950 for further study. He had recently recovered from pertussis and at a previous examination, the diagnosis of right diaphragmatic eventration had been entertained. The pertinent physical findings were dullness to percussion with absent breath sounds over the entire right

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AN UNUSUAL TYPE OF TRAUMATIC KIDNEY

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The normal location of the kidney in the lumbar gutter gives it considerable protection from direct trauma. When the organ is ectopic there is greater liability to injury.

Campbell outlined the importance of renal anomalies as follows: 1) diminished renal reserve; 2) malformation or displacement of the kidney; 3) urinary obstruction more easily results from this anomaly; 4) there is an abnormal discharge of urine; 5) this author adds greater exposure to direct or indirect trauma.

Ectopia of the kidney permits the organ to be anywhere in the abdominal or pelvic cavity when it is arrested in its passage from the embryological position to the fully developed lumbar anatomical situation. The ectopia can be either unilateral, unilateral crossed and fused to the normal organ or bilateral and also bilateral and fused. This fusion can be at the lower pole, or more rarely at the upper pole when the result in either case is a horseshoe kidney either of the classical type or the inverted type. It may also involve the entire mesial borders of the kidney when the resulting renal mass contains both pelves and is referred to frequently as the "pancake type of kidney."

Not many of the kidney anomalies are found during the course of a routine physical examination. They are only found in a urological study or accidentally, as in the following case.

This is the tenth reported case of congenital fused ectopic pelvic kidney and the first case of damage resulting from this type of injury to an anomaly.

D. L. B., a Negro aged 19 years, was admitted to the surgical service at the U. S. Naval Hospital, San Diego, California on March 29, 1951 complaining of severe pain in his abdomen. He had been well until noon that day. At that time he was carrying his mess tray (which is metal) and had the edge of the tray impinging on his abdomen at approximately the level of the navel. In passing through a door, the outside edge of the tray was struck and the proximal edge was forcefully driven against his abdominal wall. About an hour later he had severe cramps in his abdomen below the navel. He began to vomit and the pain became more severe as time went on. There was no history of any previous attacks of abdominal pain of a similar nature.

Physical examination on admission was entirely negative except for the abdomen where generalized tenderness and voluntary muscle guarding were noted. There was also a generalized rebound tenderness throughout the abdomen. No masses were found.

Laboratory studies: Complete blood count demonstrated 4,153,000 red cells; 19,200 white cells; differential count, 88 per cent neutrophils, 8 per cent lymphocytes, hemoglobin 12 gm.; hematocrit 32. Urinalysis demonstrated the urine to

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

by the patient's youth. Urological studies are probably indicated in diaphragmatic eventration for academic and practical reasons. The high kidney, when present, may interfere with the operative repair of eventration and accidental renal injury may be avoided.

SUMMARY

The causes of high renal ectopy have been discussed. Recently, an increased awareness of this condition has become evident; therefore, the authors felt the results of their observations together with a review of the literature should be presented for urological consideration. Methods for diagnosis and management have been suggested.

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Conservative treatment was recommended. The abdomen was closed and the patient made an uneventful recovery, and was transferred to the urological service for further study.

On April 3, 1951 an excretory urogram demonstrated no evidence of kidney shadows in either kidney fossa after 30 minutes had elapsed. Dye was seen in the bladder in normal concentration and a structure of indefinite radio-opacity was seen in the left side of the true pelvis which was consistent with a possible ectopic kidney. There was also a suspicious shadow overlying the right ala of the sacrum which could have been the other half of a pair of ectopic kidneys. Ureters were seen to be normal but could not be followed above the brim of the true pelvis. A retrograde pyelogram was made April 9, 1951.

A No. 24 Brown Burger cystoscope was introduced into the bladder easily. All bladder and associated structures were normal. There was no residual urine in the bladder. No. 5F ureteral catheters were passed up each ureter and they were obstructed at 15 cm.

The first x-ray of the abdomen with the catheters in place demonstrated them to pass laterally on each side and then curve medially to stop at the position of the aforementioned radio-opacities seen on excretory urography. These catheters were removed and bilateral bulb uretero-pyelograms were made (fig. 1). The ureters followed the previously described course of the ureteral catheters. The ureters then terminated in a renal pelvis on each side which overlaid the ala of each sacrum on the respective side in close approximation to each other. This finding concurred with the operative finding of bilateral ectopic pelvic fused kidney. This type of kidney is often referred to as a pancake kidney. The excretory and retrograde pyelograms did not demonstrate any evidence of urinary extravasation.

DISCUSSION

The unusually exposed and unprotected position of these kidneys left them easy prey to many types of trauma which would usually be disregarded as cause for serious urinary tract injury. Yet this man passed through childhood and young manhood without ever receiving a similar disability from any cause.

It is of considerable interest to note that when the patient entered the hospital, the history and physical findings were suggestive of rupture of an intra-abdominal viscus. Perhaps of even greater interest is the trivial type of injury which resulted in the origin of these symptoms.

When the surgeon saw the patient an abdominal exploration was recommended. The retroperitoneal hemorrhage was found to be caused by a contusion of these kidneys and not a rupture. If there was any rupture, the rupture must have been limited to the renal capsule, as it did not involve any of the collecting portions of the kidney, as demonstrated by excretory and retrograde pyelography, and the report of the urologist who palpated the renal mass warrants the diagnosis of bilateral ectopic fused kidney.

SUMMARY

The tenth case of bilateral ectopic fused pelvic kidney is here reported with a brief discussion of the literature.

be straw colored, alkaline, specific gravity 1.022, negative for albumin and sugar, 0–5 red blood cells per high powered field in the urinary sediment.

He was seen by the surgical watch and the following notation was made: The history was the same as the foregoing. He was not in shock, and not sweating or thirsty. Blood pressure 120/70; temperature, pulse and respirations were normal.

Physical examination by the surgeon confirmed the findings of the intern and added the additional notes: There were no bowel sounds of peristalsis and the surgeon made the provisional diagnosis of 1) ruptured liver, 2) ruptured spleen, 3) ruptured viscus, and advised immediate exploration of the abdominal cavity.

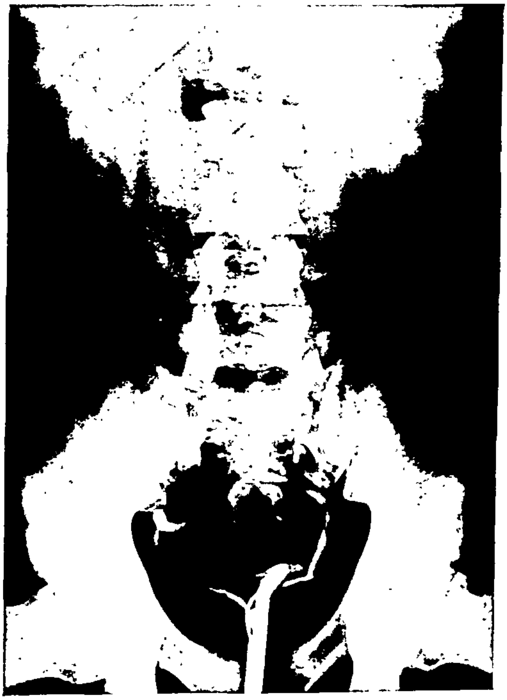

Fig. 1

Exploratory operation of the abdomen was done and the findings were noted as a retroperitoneal hemorrhage mainly to the right of the midline. It was found to originate in an injured kidney. The renal mass appeared to be of a horseshoe type, with fusion at the superior pole, but an incomplete cleft was noted between this upper pole and the renal masses were not separated at the lower pole. No involvement of the left kidney was noted. The liver and spleen were normal and there was no evidence of disease of the bowel. The renal mass was found to be lying over the sacral promontory extending to the hollow of the sacrum.

The senior resident in urology was called to enter into the operative team and examine the interior of the abdomen. He expressed the opinion that the renal anomaly was a fused ectopic pelvic kidney lying in the sacral hollow and over the promontory of the sacrum.

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FIBROMYXOLIPOMA OF THE KIDNEY

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Primary intrarenal lipomas of clinical significance are rare in individual experience. Only eighteen authenticated cases have appeared in the literature. Their origin and nature have been the subject of much study and controversy; however, they are usually classified as mixed tumors. It is the purpose of this paper to report an additional case.

CASE REPORT

Mrs. A. D., a 78 year old white woman, was admitted to the Boston City Hospital on December 13, 1949 with pain in the left upper abdomen and hematuria of 6 hours duration. In 1946, she had been treated here for a scalp laceration and on that admission, a mass was noted in the left upper quadrant, but she declined further investigation.

Examination revealed an acutely ill patient in moderate vascular collapse. There was a large, smooth, nonpulsating mass in the left abdomen which extended from the costal margin to the left anterior superior spine and medially to the umbilicus. There was a lipoma of the right shoulder.

Laboratory studies showed 3 plus albuminuria with gross and microscopic hematuria. The hemoglobin was 10 gm. per 100 milliliters and the white blood count was 16,450 per cubic millimeter. The blood urea nitrogen was 39 mg. per cent.

Cystoscopy revealed an essentially normal bladder after evacuation of existing clots. Clear urine appeared from the right ureteral orifice with bloddy jets from the left. There was no function of the left kidney after injection of indigo carmine. Pyelograms were made (fig. 1).

An x-ray series was negative for metastases. The patient was transfused repeatedly with whole blood. The mass increased in size and hematuria persisted. On December 15, 1949, a left transperitoneal nephrectomy was performed and a 910 gm. kidney removed (fig. 2). Recovery from surgery was uneventful. She was lost from follow-up after 7 months.

The pathological diagnosis was fibromyxolipoma of the kidney with extensive hemorrhage. A typical microscopic section is shown (fig. 3).

DISCUSSION

It is doubtful whether a clinical diagnosis of intrarenal lipoma can be made. These growths develop at the expense of the renal parenchyma and when sufficiently large produce the classic triad of all renal neoplasms: pain, mass and hematuria. The pyelographic changes are those of any space occupying tumor.

Intrarenal lipomas are confused most frequently with renal cell carcinoma, cyst, replacement lipomatosis, perirenal lipomas and retroperitoneal tumors.

The case history demonstrates the extreme vulnerability of such an anomalous type of kidney.

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There is a predominant female sex incidence. Lipomas elsewhere in the body are not uncommon. A mass of long duration in the absence of metastases suggests a benign lesion of the kidney. Extensive perirenal hemorrhage occurs often. The absorption co-efficient of fat is lower than that of the surrounding tissues and increased radiolucency may be expected on x-ray. At surgery, the growth is subcapsular and the renal veins are not involved regardless of the magnitude of the lesion. Despite the few distinguishing characteristics of these tumors, it must remain for the pathologist to supply the correct diagnosis.

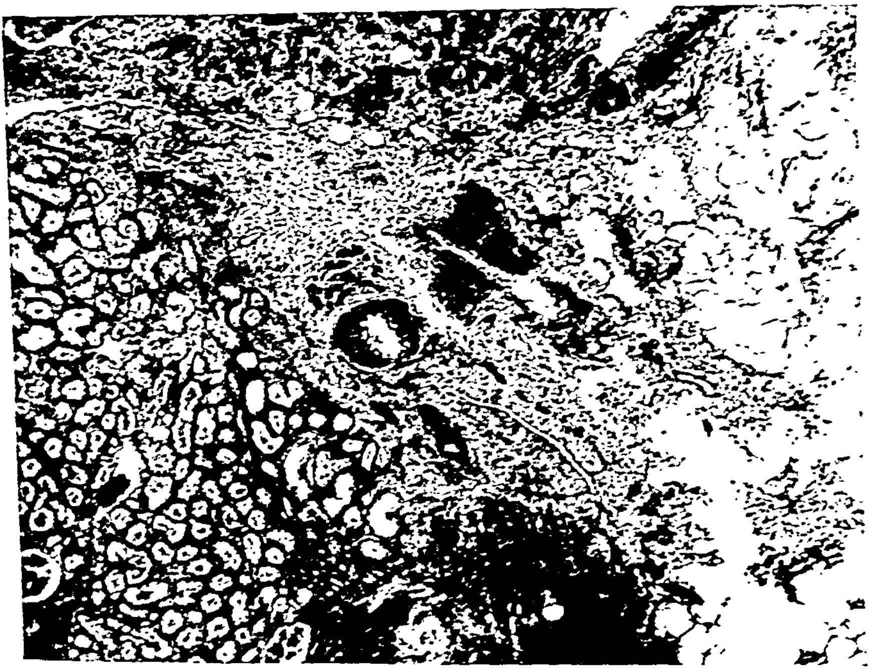

FIG. 3. Low power photomicrograph of a representative area shows adult type of adipose tissue cells.

SUMMARY

A case of renal fibromyxolipoma has been presented and discussed. A survey of the literature disclosed only eighteen authenticated cases.

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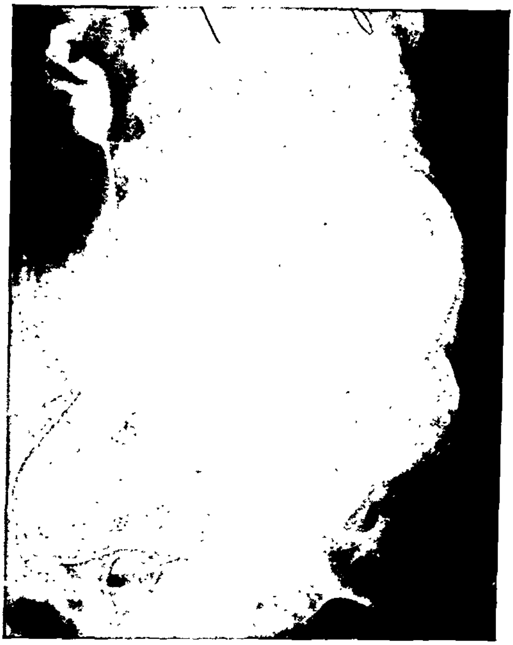

FIG. 1. Left renal elements are markedly displaced to left and rotated. There is distortion, elongation, flattening and irregularity of the pelvis and calyces. A poorly defined soft tissue mass which appears to cross the midline can be seen.

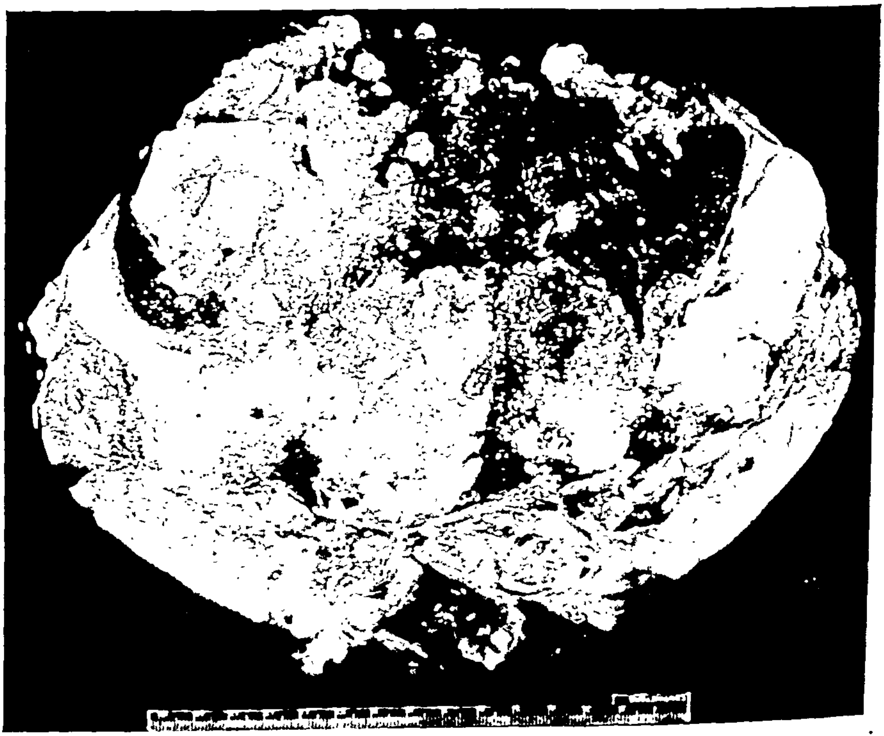

FIG. 2. Photograph of sectioned specimen shows a huge polar mass with accompanying hemorrhage replacing renal medulla.

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URETERITIS CYSTICA: TREATMENT WITH SULFADIAZINE, PENICILLIN AND AUREOMYCIN

REPORT OF A CASE

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A case of ureteritis cystica in which the lesions disappeared and a sustained remission was produced by treatment with antibiotics has been studied. Our purpose in reporting this case is, first, to offer an observation relevant to the long discussed question of the pathogenesis of this condition; and second, to record a satisfactory therapeutic response. The literature contains only a few reports of successful treatment of this disease and none which we can discover by antibiotics.

Morgagni, in 1761, described ureteritis cystica for the first time and noted its association with urinary tract inflammation. He observed "hydatids" within the ureters of two old men who had died with urinary tract inflammation associated in one case with what today would have been recognized as prostatism and in the other with posterior urethral stricture. In 1887 von Limbeck's microscopic studies showed that these lesions are multiple, small, subepithelial cysts, lined with cuboidal or transitional epithelium and anatomically indistinguishable from the structures found in cystitis cystica. In the same material he found downward sprouts of epithelium which he postulated assumed cystic form. Von Brunn, 6 years later, gave the name of cell nests to these epithelial sprouts as they appeared when separated from the parent epithelial layer.

Herxheimer, reviewing his own material and the collected observations of others in 1906, recognized epithelial sprouts, cell nests, and the cysts as progressive phases of a proliferative response of urinary tract epithelium to chronic inflammation. Giani, in the same year, reported having reproduced the lesions of cystitis cystica experimentally by inducing chronic inflammation within the bladders of rabbits. Utilizing cystoscopic observations, Hinman, Johnson and McCorkle recognized the association of cystitis cystica with inflammatory conditions of the urinary tract. Warrick successfully demonstrated bacterial infection in twenty of twenty-eight cases of the same disease, with E. coli as the commonest organism.

The development of urography has made recognition of ureteropyelitis cystica possible in the living patient. Little however is known of the natural history of the disease and from the few published reports available it is difficult to construct a characteristic clinical picture because the symptoms do not differ specifically from those of other inflammatory or obstructive lesions of the urinary tract.

The writer acknowledges his gratitude to Dr. Clyde L. Deming, Professor of Urology in the Yale University School of Medicine for aid in preparation of the report; to Dr. Arnold H. Janzen, Professor of Radiology for critical scrutiny of the radiographic evidence; and to Dr. Michael S. Hovenanian, former Instructor in Urology for guidance in management of the case.

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The findings presented by this patient were regarded as consistent with either acute pyelonephritis with or without ureteral obstruction, or acute appendicitis, and consultants agreed upon overnight observation. Seventeen hours after the pain had begun, an excretory urogram showed a normal left upper urinary tract, but tubular diodrast excretion on the right side blocked within the pelvis (fig. 1, *A*). Cystoscopy revealed an easily dilated posterior urethral stricture, moderate trigonal hypertrophy, and a right ureteral meatus which was not seen to excrete urine. The ureteral catheter (No. 5F) was introduced on the right side with difficulty. Fluid irrigated from the right pelvis contained no organisms in smear or culture, and the left kidney urine was sterile. Phenolsulfonphthalein excretion from the right kidney was nil; from the left the dye appeared in 3 minutes with secretion of 20 per cent in 15 minutes. The pyelo-ureterogram on the right showed many small spherical filling defects in the ureter with obstruction at the calyces by a similar process (fig. 1, *B*). The left pyelo-ureterogram was normal.

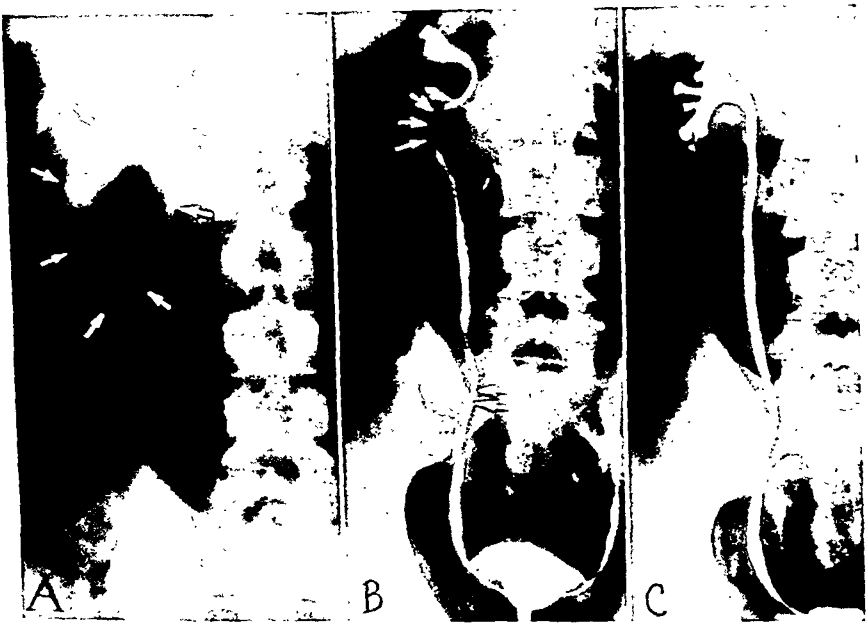

FIG. 1. *A*, excretory urogram 1 hour after injection of diodrast. Dye appears within kidney but does not fill pelvis or ureter. *B*, retrograde pyelogram. Small spherical filling defects throughout right ureter and a similar process deforming shadow of right pelvis. *C*, retrograde pyelogram after 14 days of treatment. Right upper urinary tract is now normal. Pressure of injection resulted in some pyelotubular reflux.

For the next 14 days treatment consisted of daily doses of 2.0 gm. of sulfadiazine and 1.0 gm. of aureomycin orally, and 600,000 units of procaine penicillin intramuscularly. In 36 hours the patient was free of abdominal pain and in 48 his fever had subsided. On the ninth day an excretory urogram showed normal dye excretion on both sides with disappearance of pyelo-ureteritis cystica. Retrograde examination on the fourteenth day showed normal pyelo-ureteral

It is of interest that in 1934 Hinman and his associates concluded that "the first step in the treatment of the condition is obviously the removal of the source or cause of the inflammatory process." Five years later, Burkland and Leadbetter produced symptomatic improvement in a case of pyelo-ureteritis and cystitis cystica with pure cultures of H. influenzae by treatment with sulfanilamide but could not eradicate the organism permanently from the urine. Toulson reported having treated 2 patients with ureteritis cystica with sulfaniazine without effect.

Kindall had brought about disappearance of the lesions in one case by placement of large ureteral catheters for 3 days followed by injection of silver nitrate. Kopp treated a case in similar manner with success. There are a number of reported instances of resection of the involved portion of the upper urinary tract for ureteropyelitis cystica.

Our patient was a man in whom obstruction of the calyces of the right kidney had been produced by a process identified by excretory and retrograde pyelography as typical pyelo-ureteritis cystica. The history was consistent with the presence of chronic lower urinary tract infection. Because he had been given penicillin a half day before he came under our care, bacteriologic identification of the upper urinary tract invader was impossible and a combination of drugs was used. Within 2 days he was free of fever and pain, and within 9 days urograms showed that his upper urinary tract had returned to normal. He remained well during a year of observation, at the end of which his urograms were normal and his urine uninfected

CASE REPORT

A 29 year old man (L. G., C35611) was admitted to New Haven Hospital on July 30, 1950, because of constant right lower abdominal pain radiating to the right testis accompanied by vomiting. He had had gonorrhea 10 years before admission and 2 weeks before being referred to us a second attack of the same disease had been treated with penicillin with prompt relief. Three days before he came to the hospital, burning micturition and a slight urethral discharge had recurred. A short time after the onset of his pain on the day of admission he had been seen by a physician who had found gonococci in a smear of the prostatic secretion and administered an injection of penicillin. Because of persistent pain and vomiting he came to the hospital 6 hours later.

At the time of admission he was uncomfortable and flushed. Temperature was 99.4 orally, pulse 90 and blood pressure 136/102. Abnormal physical findings were otherwise limited to deep tenderness in the right hypogastrium. His red blood cell count was 6.0 million, hemoglobin 16.0 gm., white blood cell count 14,000 with 85 per cent polymorphonuclear forms, 12 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The urine was of amber, smoky appearance, with a pH of 8.0, and contained no albumin or sugar. One hundred red blood cells and 5 white blood cells were seen in the high power field of the centrifuged sediment although no organisms were noted in the stained smear or subsequently reported in cultures. The blood nonprotein nitrogen and an x-ray of the abdomen were normal.

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PRIMARY BENIGN NEOPLASM OF URETER ASSOCIATED WITH URETERAL CALCULUS

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Fewer than 40 cases of primary benign neoplasm of the ureter, substantiated by microscopic examination, have been reported in the literature. Of these, only a small percentage have been associated with ureteral calculi.

It is the purpose of this paper to report an additional case of primary neoplasm associated with calculus.

CASE REPORT

B.M., a 47 year old luncheonette counterman and former pugilist, was referred to me by his physician on February 14, 1950, because of microscopic hematuria. He complained of vague, dull abdominal and left loin pain of 1 year's duration. He had chronic, severe low backache for 5 years. One year previously he had received treatment for several months by an orthopedist because of backache, but the pain, nevertheless, persisted. During this period, the patient recalled that he had several episodes of nocturia up to three times, which would last for several nights and then disappear spontaneously.

In August 1949, there was an attack of severe left loin colic. He consulted a physician, who found microscopic hematuria. The patient states that he then consulted a urologist in another city, who, after doing physical and cystoscopic examinations and taking a scout film, told him that he had probably passed a small stone.

The abdominal and left loin pain and the backache persisted. His family physician examined the urine on several occasions during the next 4 months, and each time found microscopic hematuria.

The patient also stated that he had been having episodes of pain in his great toes for several years, and that this had been diagnosed as gout.

Physical examination revealed a husky, well developed man in no acute distress. Several small, whitish tumors were noted on the lobe of each ear, and these presumably were uric acid tophi. No abdominal or loin masses were present and no tenderness in the costovertebral angle. The genitalia appeared normal. The prostate was slightly enlarged, smooth, boggy and nontender.

The urine was smoky. Acid reaction. Specific gravity 1.018. Albumin, slight trace. Sugar, negative. Microscopic examination: specimen was loaded with red blood cells.

Excretory urography disclosed a tiny calcareous shadow in the region of the left ureter at the level of the interspace between the third and fourth lumbar vertebrae. The dye appeared in both kidneys within five minutes. No structural changes were detected in either the left or right kidney. In the 15 and 30 minute films, a filling defect was noted in the middle third of the left ureter. The right ureter appeared normal.

Cystoscopy and left retrograde pyelography were done under caudal anesthesia. The bladder appeared normal. A No. 6 ureteral catheter was passed 10 shadows (fig. 1, *C*), no infection in either kidney, and normal phthalein excretion from both kidneys. At the end of a year, during which he had remained well, the patient permitted examination by excretory urography which was normal. The urine remained sterile.

SUMMARY

A case is reported in which renal obstruction was produced by pyelo-ureteritis cystica on the right side. Under treatment with sulfadiazine, aureomycin and penicillin there was prompt relief of obstruction and disappearance of the lesions. After a year the upper urinary tracts remained normal.

Evidence in this case corroborates the inflammatory pathogenesis of pyelo-ureteritis cystica and suggests that further trials of antibiotics may be warranted in this condition.

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an elliptical incision. A No. 8 ureteral catheter was passed through the ureterotomy down to the bladder and then up to the pelvis without meeting obstruction. The catheter was then removed, and the ureterotomy closed with 000 plain catgut sutures. A Penrose drain was placed down into the wound and exteriorized posteriorly. The incision was then closed in layers.

There was a temperature rise to 101.6F on the first postoperative day. Thereafter, the temperature remained normal. The patient was out of bed on the second day, and the wound was dry by the eighth postoperative day. He was discharged on the tenth day completely asymptomatic.

Pathologist's report (Dr. Arthur Schifrin): The gross specimen was a pea sized polypoid structure measuring 1 cm. in height and 0.6 cm. in width. It was of soft consistency. On section the base measured 0.5 cm. in width. The polyp consisted of gray-pink, soft, homogeneous tissue which was sharply demarcated from the submucosal area. The lesion was resected 0.4 cm. deep to the polyp and closest circumferential edge was 0.3 cm. from the polyp. In addition, a fragment of the adjacent ureteral wall and a grape seed sized tan colored calculus were removed.

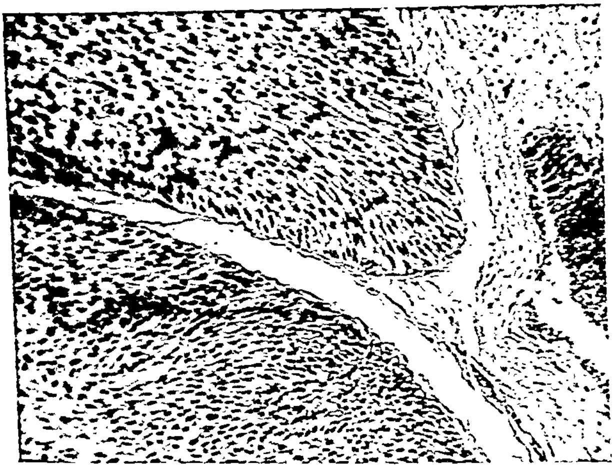

FIG. 2. Benign papilloma of ureter. Note sharp demarcation from stroma. (X 200.)

On microscopic examination (fig. 2) the tumor had a polypoid papillary architecture and was lined by regular transitional epithelium with regular nuclei. No frank nuclear atypism, nuclear bizarreness or mitoses were seen. The basal layer of the epithelium was sharply demarcated from the stroma which contained several large dilated congested blood vessels.

Study of the adjacent ureter wall showed that the surface of the lumen was lined by regular transitional epithelium with regular nuclei. The basal layer was sharply defined. The submucosa was edematous and congested. The muscular layer was well developed. No infiltration of the wall by tumor tissue was noted. Diagnosis: Benign transitional cell papilloma of ureter; adjacent wall, free of tumor tissue; ureteral calculus, which consisted of uric acid, ammonia and calcium oxalate.

cm. up the left ureter, and a gravity pyelogram made (fig. 1). Dye came back into the bladder around the catheter after approximately 5 cc of 40 per cent hippuran, colored blue with indigo carmine, had passed through the catheter. The catheter was then passed to 20 cm. without meeting obstruction or noticeable bleeding.

The patient was admitted to the Park East Hospital, New York City, on February 24, 1950 (admission 6098). The preliminary diagnosis was 1) tumor of the left ureter; 2) left ureterolithiasis.

Urinalysis revealed 5–8 white blood cells per high power field. No red blood cells. Hemoglobin 5,400,000. White blood cells 10,600. Urea nitrogen 9 mg. per cent. Blood uric acid 3.3 mg. per cent. Serology was negative.

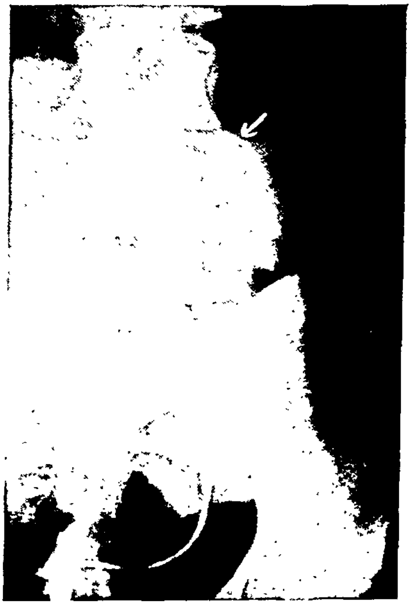

FIG. 1. Retrograde pyelogram done by gravity method

A scout film taken on the day of admission again showed a small calcareous shadow in the region of the left ureter between the third and fourth lumbar vertebrae.

Operation was done February 25 under spinal anesthesia. With the patient placed on his side in the usual kidney position, a left loin incision was made exposing the midportion of the ureter. A soft, fusiform enlargement of the inferior portion of the middle third of the ureter was noted. A 1 cm. incision was made through the wall of the ureter at the greatest diameter of the enlargement. As this incision was made, a grape seed sized, tan colored, smooth calculus popped out into the wound. A polypoid mass, which was attached to the wall of the ureter by a pedicle, protruded through the ureterotomy wound.

The pathologist was called to the operating room to examine the tumor in situ. It was his opinion that it was benign.

The tumor was removed complete with its pedicle and surrounding wall by

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SEPARATION OF THE URETHRA FROM THE BLADDER DUE TO FRACTURE OF THE PELVIS

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Separation of the urinary bladder from the urethra with extraperitoneal extravasation constitutes a urologic emergency. It portends certain death for the patient unless immediate surgical intervention is accomplished. With the increasing incidence of automobile accidents, the number of fractured pelves has become increasingly more common. About 10 per cent of patients with fracture of the bony pelvis, according to Key and Conwell,[1] have, also, serious injury to the lower urinary tract. McCague and Semans[2] report a 17 per cent incidence of rupture of the urethra or bladder complicating fracture of the pelvis. Harrison[3] reports a group of 160 patients with fracture of the pelvis in which there were 9 patients whose fractures were complicated by rupture of the membranous urethra and 4 with rupture of the bladder, an incidence, altogether, of 8 per cent. A careful estimate of the status of the lower urinary tract is of utmost importance, then, in *all* cases of fracture of the pelvic bones.

TYPE OF INJURY

A crushing injury, which fractures the pubic rami and causes an appreciable separation of the symphysis pubis, is the type of injury which, in our experience, is likely to tear the triangular ligament and rupture the membranous urethra. The sharp ends of the bony fragments may lacerate the bladder wall as well. The four cases presented in this report are all boys struck down by motor vehicles. The pelvic fractures sustained are diagrammed below (fig. 1). All show unilateral fractures of both pubic rami and appreciable separation at the symphysis.

EXTENT OF EXTRAVASATION

It is well known that when extravasation occurs *above* the triangular ligament from rupture of the urethra or bladder, the escaping urine and blood invades the perivesical tissues and infiltrates the retroperitoneal and ischiorectal spaces (fig. 2).

According to Culp,[4] the triangular ligament, chiefly the dense anterior layer, prevents extension into the perineum and adjoining structures.

Extravasations *below* the triangular ligament follow Buck's and Colles' fascia. This potential space for the accumulation of extravasated fluid extends into the perineum, scrotum, penis, and abdominal wall. The attachment of Scarpa's

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Read at a meeting of the New England Section, American Urological Association. Boston, Mass., November 8 1951.

[1] Key, J. A. and Conwell, H. E.: Fractures, Dislocations and Sprains. C. V. Mosby Co. 1942.

[2] McCague, E. J. and Semans, J. H.: J. Urol., 52: 36-41, 1944.

[3] Harrison, J. H.: Surg. Gynec. & Obst., 72: 622-631, 1941.

[4] Culp, O. S.: J. Urol., 48: 266-286, 1942.

There has been no recurrence of low backache, no microscopic hematuria or vague abdominal and left loin pain since the operation. Excretory urography was done on March 18 and also October 16, 1950. Normal urograms were obtained both times. The patient was last seen on August 11, 1951, at which time he had no symptoms, and the urine was normal.

DISCUSSION

The diagnosis of ureteral neoplasm in this case was made on the presence of a large filling defect which could be detected by both excretory and retrograde pyelography.

The possibility of nonopaque uric acid calculi in the ureter in this patient, who had a history of gout, was entertained, but the easy passage of a No. 6 ureteral catheter past the large filling defect seemed to preclude such a diagnosis.

On the other hand, the lack of profuse bleeding, particularly after instrumentation of the ureter, was unlike the usual ureteral neoplasm. The association of an opaque calculus with the main lesion was proven preoperatively by the excretory urogram with exposures taken in the anteroposterior and oblique positions.

The bizarreness and unusual behavior of the lesion to instrumentation prompted me to explore the ureter before proceeding with radical surgery. The benign appearance of the polyp, the softness of the wall and the opinion of the pathologist at the operating table led to conservative surgery.

Ureteronephrectomy has been advocated as the procedure of choice for ureteral neoplasm, whether malignant or benign. In the past few years, several dissenting opinions have been voiced. The objection to conservative surgery of benign lesions has been theoretical. It has been said that if a benign lesion were allowed to stay in the ureter long enough, it would become malignant. Perhaps so, but if the lesion is removed while still in the benign stage, does the potentiality to malignancy still remain?

Actually, there has been no adequate clinical study of patients who have had conservative surgery.

In the operation performed on this patient, an elliptical section of the dilated ureteral wall which contained the pedicle of the polyp was excised, and the opening closed in the usual manner as for any ureterotomy. This simple procedure has appeared to be adequate in this case.

SUMMARY

A case of primary benign ureteral neoplasm associated with ureteral calculus is presented.

A suggestion is made that conservative surgery may be adequate for the treatment of benign primary tumors of the ureter.

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petent and at operation a bladder filled with clear urine is found. This feature may be exaggerated by strenuous intravenous therapy given preoperatively for the shock. Ecchymosis of the abdominal wall, genitalia and perineum may soon become apparent. This is evidence of extravasation below the triangular ligament.

The patient usually has a strong desire to void but is unable to do so. Frank blood is present at the external urethral meatus. Attempts to pass a catheter per urethram to the bladder are unsuccessful and but a few drops of bloody fluid come through the catheter. No irrigating fluid should be used at this point. However, this *is* the time to inject, retrograde, a small amount, 15–30 cc, of radio-opaque solution (skiodan) and to take an x-ray. An attempted cysto-urethrogram done at this time will make the diagnosis certain if any doubt exists on the basis of clinical findings alone. The medium usually assumes a sunburst like appearance, described by Weens.[5] The end of the catheter may show up in strikingly bizarre positions on the film (fig. 3, *A*). In some cases, if the shock is easily controlled, excretory urography can be helpful. In the excretory urogram, if sufficient contrast medium shows up in the bladder, an elongated pear shaped or tear-drop deformity of the bladder, described by Prather and Kaiser,[6] may be seen, riding much higher than its usual location (fig. 3, *B*).

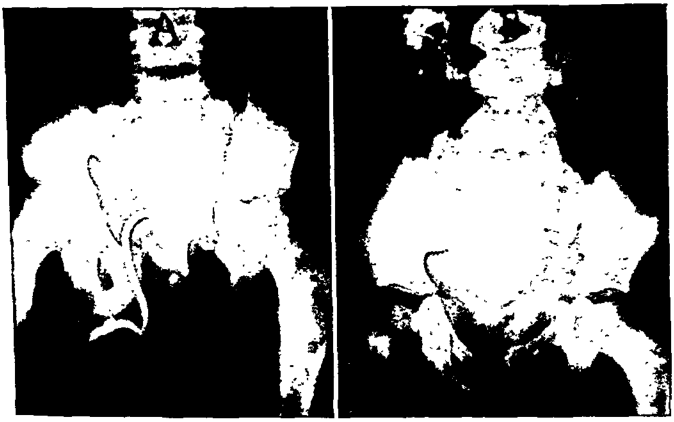


FIG. 3. *A*, case 4 showing extravasation of dye (skiodan) and bizarre position of catheter. *B*, case 3 showing teardrop bladder shadow riding high above normal position, demonstrated by excretory urogram.

Attempted cystoscopy is of little or no value and can add immeasurably to the trauma already present without contributing any worthwhile information. Rectal examination has been recommended as a valuable aid in helping to make the diagnosis.[3] Collections of extravasated blood and urine can be detected by this means, as well as a change in position and mobility of the prostate. Rectal examination was not done in our cases and is probably of less value in children than in the adult male.

[5] Weens, H. S., Newman, J. H. and Florence, T. J.: New Eng. J. Med., **234**: 357–364, 1946.

[6] Prather, G. C. and Kaiser, T. F.: J. Urol., **63**: 1019–1030, 1950.

fascia to the fascia lata at the level of Poupart's ligament prevents extension to the thighs.

The first three of our cases showed extravasation above the triangular ligament only. The fourth case gave evidence of extravasation both above and below that boundary.

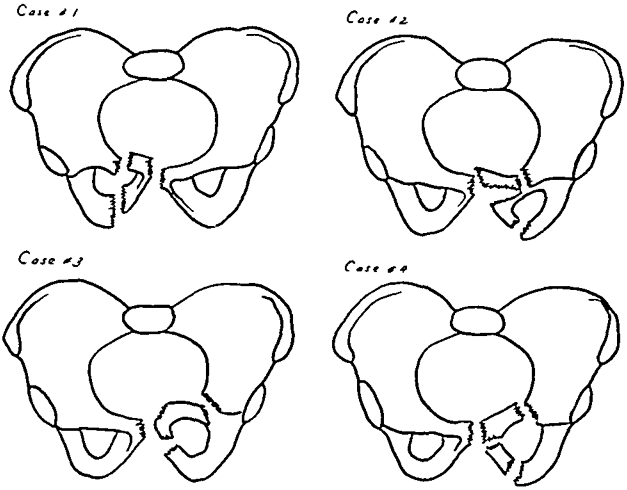
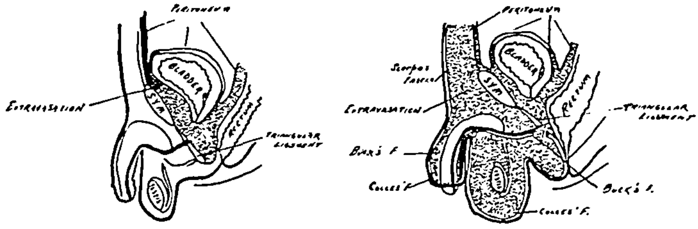


FIG. 1. Schematic representation of pelvic fractures, all showing unilateral fractures of both pubic rami and appreciable separation at symphysis.



EXTRAVASATION ABOVE TRIANGULAR LIGAMENT

EXTRAVASATION ABOVE and BELOW TRIANGULAR LIGAMENT

FIG. 2. Diagrammatic representation of two types of extravasation recognized in cases reported. (Redrawn from article by O. S. Culp, J. Urol., 48: 266–286, 1942.)

DIAGNOSIS

Early diagnosis is important in these cases. It has been stated by Harrison[3] that a mortality rate of 20 per cent occurs in cases treated within the first 12 hours after injury. After that period, however, the mortality rises sharply to 85–90 per cent.

The diagnosis of fractured pelvis with rupture of the urethra is not difficult. Shock is usually present. Pain is severe on movement of the lower extremities. Compression of the pelvis causes pain and frequently crepitus is elicited. The suprapubic area is exquisitely tender and may bulge for two reasons: because of the extravasated fluid and in some cases because of a distended intact bladder riding high above the symphysis. The internal sphincter remains quite comappears early, and must be combated in the usual manner. Electrolyte balance must be watched carefully. In our case 4, a potassium deficiency, unrecognized early was treated successfully after the patient called our attention to it by having a convulsion.

With the co-operation of our orthopedic colleagues and the use of sling traction the pelvic bones must be adequately cared for.

Suprapubic drainage should be maintained 2–4 weeks, urethral catheter drainage 6–8 weeks.

CASE REPORTS

The following case reports illustrate some of the features of diagnosis and treatment just described.

Case 1. L. Z., a 4 year old boy, was admitted to the hospital on March 26, 1943. He had been struck by a coal truck a few minutes before entry. A trickle of blood was seen coming from the external urethral meatus. He was in moderate shock. He complained of pain in his lower abdomen and was unable to void. The lower abdomen was protuberant, tender and spastic. The genitalia appeared normal. An attempt to catheterize the patient was unsuccessful. An x-ray of the pelvis showed a fracture of the upper and lower rami of the right pubic bone. After shock therapy was instituted the patient was taken to the operating room. The bladder was approached through a suprapubic incision. Considerable bloody fluid was suctioned from the cave of Retzius. There was a wide separation between the two ends of the torn membranous urethra. Clear urine was seen to spurt from the ¾ inch length of proximal urethra still remaining attached to the bladder. The bladder was opened and showed nothing but clear urine. The continuity of the urethra was reestablished with a No. 8 catheter using traction with a rubber tissue drain wrapped around the proximal end of the catheter as described above. The bladder was closed around a de Pezzer catheter which emerged from the abdominal wound together with a long silk thread tied to the nose of the urethral catheter. Both catheters drained for 4 weeks at which time an abscess formed at the penoscrotal junction. This was incised and drained. The depth of the abscess cavity communicated with the urethra. At this time the suprapubic catheter was removed and the urethral catheter changed. The urethral catheter stayed in another 4 weeks at which time both the suprapubic and abscess wounds healed.

The patient has been followed at intervals since. Attempts to dilate the urethra were not entirely satisfactory. A cysto-urethrogram done on September 15, 1951, eight and one-half years postoperative, shows the reason for this. There is a diverticulum the size of a walnut at the penoscrotal junction (fig. 4, A). The boy is asymptomatic, attends school, runs and plays normally, voids without frequency and nocturia, and with a good forceful stream.

Case 2. H. C., a 6 year old boy, was admitted to the hospital on January 26, 1946, a few minutes after being run down by a truck while coasting on his sled. On entry a blood clot was seen in the external urethral meatus. I ined of pain in his lower abdomen, had the desire to void but could ale, disoriented and in moderate shock. The entire abdomen was stic,

TREATMENT

Treatment, when the patient is first seen, must be directed primarily against the shock or he may not live long enough to receive the benefit of surgery. Intravenous fluids, including plasma and blood, should be given as soon as possible. Opiates for the pain, careful handling and immobilization of the fractured pelvis will help to avoid increasing the shock.

As soon as these measures to combat the shock have begun to have their desired effect, and the diagnosis has been made, the patient must be operated upon at once.

The surgical approach should be through a suprapubic midline incision. Blood, both clotted and fluid, will be found in the perivesical tissues, in the retroperitoneal area, and filling the space of Retzius. After the blood is suctioned off and mopped out, and some degree of hemostasis is established, the bladder should be identified. This may not be easy. If intact and distended, it will be found riding well above the symphysis pubis, its distal end torn loose from the urethra, usually at the apex of the prostate. There is often a wide separation of the two ends of the urethra. If the bladder wall is lacerated, also, as occurred in our case 4, it is, of course collapsed and may require considerable ingenuity to reconstruct it. If the bladder is intact, it should be opened with a longitudinal midline incision down to but not including the bladder neck. A Foley type catheter of appropriate size should then be passed retrograde per urethram. A stylet may be necessary. The proximal end of the catheter should then be guided through the space of Retzius, through the bladder neck, into the bladder and its balloon inflated. A long silk thread passed through the nose of the catheter and tied, with the long ends emerging through the suprapubic wound, allows necessary control for later catheter changes and in the event of possible rupture of Foley bag. This is an important feature.

With traction on the Foley catheter the severed urethra is approximated, or nearly so, and maintained in this position. No sutures are necessary in the urethra which appears to heal rapidly around the catheter. The bladder is then closed around a de Pezzer tube. The cave of Retzius is drained. Occasionally a pack is necessary to control persistent venous bleeding, as in our case 4. Elevation and internal fixation of the pubic bone fragments may be necessary to avoid further trauma to soft parts postoperatively.

When our first 3 cases were done, Foley catheters of small enough caliber were not available to us. However, the same principle of traction was used by wrapping a rubber tissue drain around the end of a straight catheter just distal to the eyes of the catheter. The rubber drain was transfixed to the catheter with silk ligature, then pulled down against the neck of the bladder. However, this necessitated removing this urethral catheter in about 2 weeks by pulling on the silk thread in the nose of the catheter emerging from the cystotomy wound.

POSTOPERATIVE CARE

Postoperatively, appropriate chemotherapy and antibiotics minimize the infection which was such a hazard in these cases in bygone days. Paralytic ileus healed promptly and one week later the urethral catheter was removed. The patient was discharged walking and voiding normally 8 weeks postoperatively.

This patient was not seen again until September 28, 1951, 5½ years postoperative, at which time a cysto-urethrogram was done (fig. 4, *B*). He voids without frequency and nocturia, without complaint, and was seen to have a stream of normal force and caliber.

Case 3. D. W., a 6 year old boy, was admitted to the hospital August 20, 1946, a few hours after having been in an automobile accident and after having been treated at another hospital for shock. Blood appeared at the urethral meatus. His lower abdomen was tender and tense. He had severe pain on compression of the pelvis and movement of the legs.

An excretory urogram taken on entry showed unilateral fractures of the superior and inferior rami of the left pubis with separation of the symphysis. The tear-drop bladder considerably elevated from the floor of the pelvis gave sufficient evidence of separation of the bladder from the urethra without retrograde studies.

At operation the perivesical tissues were so infiltrated with bloody fluid that the bladder was difficult to identify. Once opened, essentially the same operation done on the previous 2 cases was performed.

Suprapubic and urethral catheter drainage was maintained for 2 weeks, at which time the suprapubic catheter was removed. The urethral catheter was removed 2 weeks later. The patient was discharged voiding normally 5 weeks after operation.

He was not seen again until October 13, 1951, 5 years postoperatively, at which time cysto-urethrograms were done (fig. 4, *C*). He voids with a normal stream without frequency or nocturia. He walks and runs normally.

Case 4. C. F., a 13 year old boy, was admitted on August 22, 1951, a few minutes after being run over by a truck. He was in severe shock and complained of pain in his lower abdomen. He was unable to void. The abdomen from the umbilicus to the symphysis was protuberant, tense and had taken on a bluish discoloration which increased under observation. Ecchymosis and swelling extended to the penis, scrotum and perineum stopping at an irregular line between the scrotum and anus. A small amount of blood appeared at the external meatus. A catheter was introduced but no urine was obtained. The catheter was left in place and while shock therapy was being administered, x-rays were taken with a portable machine. Unilateral fractures of the superior and inferior rami of the left pubic bone were demonstrated. Skiodan (30 cc) was introduced retrograde through the catheter. This appeared outside the bladder in an irregular shadow characteristic of extravasation.

At operation not only was the urethra divided as in the previous 3 cases, but the left lateral wall of the bladder was widely torn, a laceration 10 cm. in length, by the sharp fragments of the fractured superior ramus. Bleeding was profuse and could be controlled only by packing. The bladder was repaired and closed around a de Pezzer catheter after continuity of the urethra was established. This was done by passing a Foley catheter retrograde per urethram and into most marked in the suprapubic region. Ecchymosis of the lower abdomen was present, and dullness to percussion below the umbilicus. He had severe pain on motion of the lower extremities. Severe pain was elicited on compression of the pelvis. The genitalia appeared normal.

Shock therapy was given. X-rays of the pelvis showed unilateral fractures of both horizontal and inferior pubic rami on the left with separation of the symphysis. A catheter was passed per urethram but no urine was obtained. Skiodan (30 cc) was injected retrograde. A large soft tissue shadow was demonstrated filling the greater part of the pelvis, its upper level at the lower border of L-4. The contrast medium, however, gave a sunburst-like shadow representing extravasation below this large soft tissue shadow which represented the distended intact bladder severed from its normal connection with the urethra. The catheter was seen looped above the contrast medium.

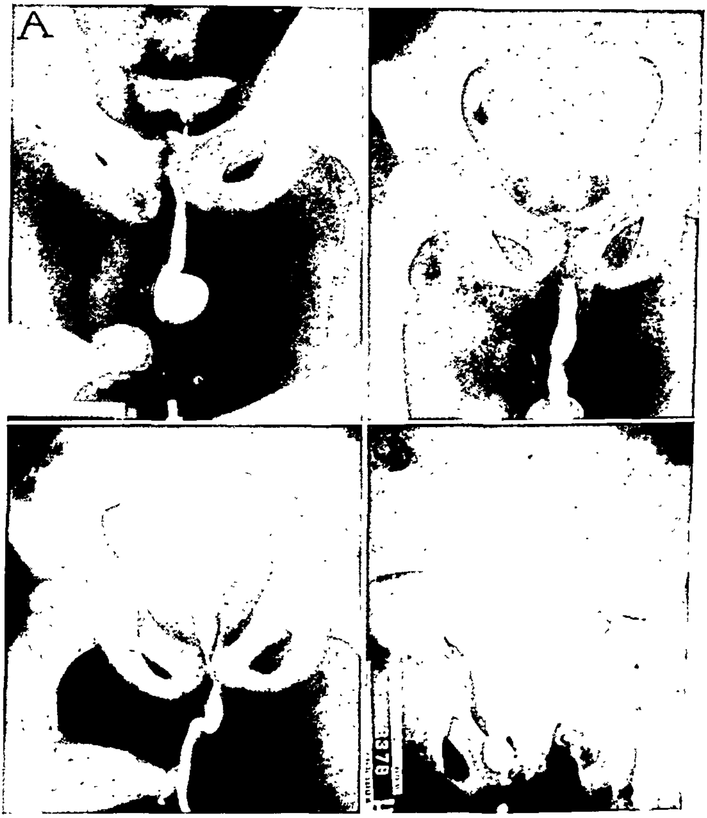


FIG. 4. *A*, case 1. Cysto-urethrogram 8½ years postoperative. *B*, case 2. Cysto-urethrogram 5½ years postoperative. *C*, case 3. Cysto-urethrogram 5 years postoperative. *D*, case 4. Cysto-urethrogram 2 months postoperative.

The patient was taken to the operating room. Essentially the same operation was done and similar findings noted as in case 1.

Both urethral and de Pezzer catheter drainage were maintained for 4 weeks at which time the suprapubic catheter was removed. The suprapubic wound

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A NEW SIMPLIFIED TECHNIQUE FOR A SINGLE-STAGE CYSTOPROSTATOVESICULECTOMY

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It has been a matter of the greatest interest among urologists all over the world to find a method to be applied in cystoprostatovesiculectomy by which this operation could be performed in one single surgical act and this way attain the ideal in modern surgery: rapidity, simplicity and efficiency.

To this day, the greatest part of the specialists has been performing this intervention dividing it into two acts, i.e., first the ureterosigmoidostomy (cutaneous implantation); and second, as a rule through the abdominal or abdomino-perineal path, the vesiculoprostatocystectomy.

When performed by specialists, the cutaneous implantation and the cystectomy are often simultaneous—and rather more rarely the ureterosigmoidostomy and the cystectomy are combined. When the latter is performed, the operation becomes extremely prolonged. The method we now present for a single act cystoprostatovesiculectomy and intestinal implantation offers the following characteristics: 1) The surgical intervention is performed in one single act. 2) Two very long interventions are reduced to a single one. 3) The minimum intervention time of only one hour, if the importance of this operation is borne in mind, is attained. 4) The intestinal implantation is reached through an extraperitoneal path. 5) The postoperative time is remarkably short. 6) The patient is not deprived of a normal social life, free from being constantly soaked in urine.

In our opinion these advantages are brought about through a careful and logical timing of the surgical stages.

TECHNIQUE

The opening of the abdominal wall is carried out by means of a vertical, a medium or an enlarged Pfannestield type incision. Were a larger operative field necessary, the Czerny modification would serve this purpose.

The bladder is "extraperitonized" in order to liberate its posterior-superior face, proceeding to the sewing of the peritoneal opening and so carry on throughout the whole operation away from the peritoneal cavity.

Immediately afterwards the ureters are laterally and extraperitoneally sought for and cut as low as it is possible. The polyvinyl or Nelaton catheters are introduced into the proximal ends of both ureters, the section of former varying according to the diameter of latter. The catheters' distal extremities are mounted on the "portabalines" following Professor A. de la Peña's technique, a technique which we have been applying in the ureterosigmoidostomy. The catheter is fixed on the ureter by transfixion using fine silk thread.

The so prepared ureters are left protruding above the abdominal incision not having thus to worry them any more until the last stage of the intervention is reached (fig. 1, A).

the bladder on a stylet, inflating the balloon and exerting traction on the catheter.

Postoperative ileus was a real problem in this case, and was finally overcome by Miller-Abbott tube drainage. Electrolyte balance and proper nutrition were also of serious concern. These have been finally corrected and the patient is now definitely convalescent. The suprapubic catheter was removed in the fourth week and the urethral catheter in the eighth week. A cysto-urethrogram was done on October 25, 1951, two months postoperative (fig. 4, *D*). He is now voiding with a good stream, with some frequency (every 2–3 hours), and has nocturia twice. There is some stress incontinence.

SUMMARY

The type of injury which will cause separation of the bladder from the urethra with extraperitoneal extravasation is described. The symptoms, methods of diagnosis, and treatment are discussed. Four cases of very similar pathological changes are reported with follow-up cysto-urethrograms, 8½ years, 5½ years, 5 years and 2 months postoperative. No deaths occurred.

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the threads to the patient's thighs (fig. 2). The implantation can be performed in any point of the anterior wall of the rectum. If it is so desired, the implantation may be done in a higher point pushing the bottom of the peritoneal block.

This stage, as well as the previous one—extraperitoneal preparation of the ureters—are in our opinion, the stages which up to now have not been properly timed, a reason that comes to explain the necessity of two separate interventions with the disadvantages involved.

Once the intestinal implantation has been carried out, it is only necessary to leave two compresses holding and protect the peritoneal suture for a few days and close the incision.

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The liberation of the cystoprostatovesical block is continued along the prostatic peak, cutting the posterior urethra, after duly binding or coagulating any vessels that might be bleeding. Then the blunt separation of the rectum, prostate, seminal vesicles, and the deferring ducts takes place, finding at last the already liberated surface of the bladder. When dissecting the bladder, the prostate and the spermatic vesicles, it is necessary to bind the vascular pedicles, as it is the case in any other total cystectomy.

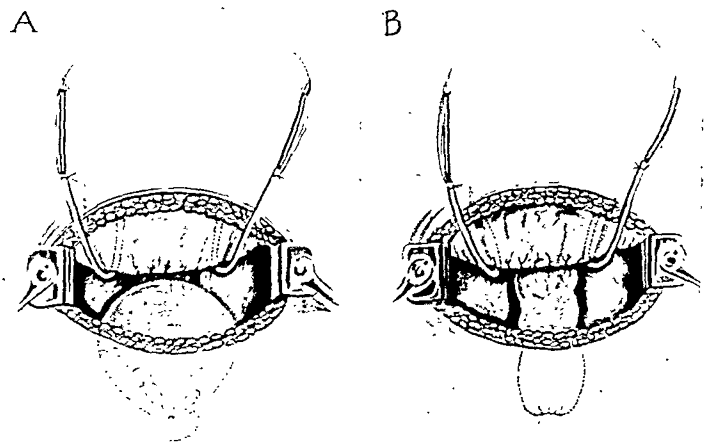

FIGURE 1

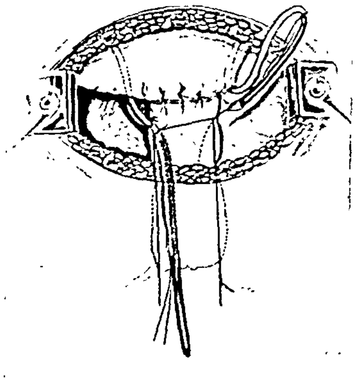

FIGURE 2

Once the piece has been extirpated the anterior wall of the rectum will be found and the already prepared ureters will be protruding from the incision (fig. 1, *B*).

Only one assistant is then needed to introduce a rectoscope and so allow the surgeon to perforate the anterior wall of the rectum with the malleable "tiller" and the rectoscopist to pull from latter and from the distal ends of the threads. The rectoscopist then takes off the "bullet" and the malleable "tiller" and fixes genitosomia, in one of which there was also gynecomastia. The most apparent change in adults was gynecomastia, but this occurred in only three.

These tumors are most likely to be confused with arrhenoblastoma, adrenal cortex rest and Sertoli cell tumors. It is generally agreed that interstitial cell tumors are at least potentially endocrine in activity. According to Teilum,[3, 4] the lipids present in Leydig cells are considered intimately connected with the production of androgenic hormones. He pointed out that there may be marked hyperplasia of the Leydig cells with almost complete absence of lipid staining material while estrogen secreting Sertoli cells of the tubules may be loaded with this substance, creating in effect a marked estrogenic predominance despite Leydig cell hyperplasia. This may be evidence that a tumor of interstitial cells may not necessarily produce androgenic substances in excess. Also there is no final proof of unmixed hormone production. These postulates facilitate an attempt to explain the phenomena of macrogenitosomia in all the young boys, gynecomastia in one of these, gynecomastia in some adults with little or no change in the genitalia or sexual drive, and the complete absence of endocrine manifestations in most of the adults.

The factors involved in the diversified endocrine manifestations may possibly be 1) interaction of the hormones of the gonads, adrenal and pituitary, particularly the latter; 2) genetic differences in the individual as well as the species; 3) cellular lipid content; 4) minor chemical variations of the various hormones produced from the gonad and the adrenal allowing for similar effects, and 5) the production of more than one hormone from the tumor.

It is believed that breast development is controlled primarily through the hormones of the pituitary as hypophysectomy prevents breast development entirely. It is known that estrogens and progesterone cause breast development through stimulation of the pituitary which secretes a mammogenic hormone. The use of testosterone therapeutically has resulted in breast development in the male. The use of adrenocortical extracts sometimes produces gynecomastia as does chorionic gonadotropin therapy. Gynecomastia develops in certain adrenal lesions and in hepatic disease and malnutritional states with Vitamin B deficiencies, the latter two conditions presumably resulting from a decreased inactivation of estrogen. It is seen during the early stages of male puberty. Thus gynecomastia may develop as a result of pituitary stimulation by either estrogenic, androgenic or adrenal cortical stimulation.

There has been much conjecture that genetic differences among individuals may provide for a variability in response to the various hormones. By appropriate breeding, differences in genes associated with one single metabolic fault involving a specific amino acid have been demonstrated. If this be true, then the conjecture has validity.

Allusion has been made to the presence of lipid granules within the interstitial cells of the testicle. Evidence has been presented that this represents an androgenic substance. Furthermore, a variation of lipid content has been demonstrated

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[3] Teilum, Gunnar: Acta path. et microbiol. Scandinav., **23:** 252, 1946.

[4] Teilum, Gunnar: Acta endocrinol. **4:** 43, 1950.

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INTERSTITIAL CELL TUMORS OF THE TESTICLE

A REPORT OF THREE CASES

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Interstitial cell tumors of the testicle merit reporting because of rare occurrence and unique behavior when contrasted with other tumors of the testicle. The major purpose of this paper is to tabulate those cases reported in the literature in which little doubt exists as to authenticity, as well as to add three more—two personal cases and third presented through the courtesy of Dr. Richard Peterfy.

The striking difference between these tumors and other testicular tumors is that they are generally benign and that often they radically affect the sexual appearance of many patients. The endocrinological manifestations of this tumor are variable except in children of prepuberal age in all of whom macrogenitosomia has been reported. In adults there are seldom apparent endocrinological changes, while in some gynecomastia develops.

As the name implies, the tumor arises from the interstitial cells of the testicle—the cells of Leydig. Hyperplasia of these cells is more frequently recognized. Perplexity must arise as to the degree of hyperplasia to be defined by the term "tumor". An adequate description of the interstitial cell is furnished by Melicow, et al.[1] Interstitial cells, numerous in fetal life perhaps a result of circulating maternal chorionic gonadotropins, greatly decrease at birth, again increasing at puberty, following which they gradually diminish in number although the size, granule and pigment content increase to the age of forty.

According to Warren and Olshausen,[2] hyperplasia generally occurs under conditions which cause a decrease in spermatogenesis, such as vasectomy. x-ray radiation, during the administration of certain glandular extracts, senile atrophy of the testes and certain acute illnesses. Occasionally there is difficulty in discriminating between hyperplasia and tumor. It is believed that tumor may result from proliferation of interstitial cells. Frequently the tumor appears to be encapsulated as though it could be shelled out with ease. It is brown to bright yellow in color. Its cells have the general appearance of the normal interstitial cell except that they are usually smaller and appear in cords with a liver-like, and at times an adrenal-like appearance.

Thirteen cases were in those under the age of 15, in ten of which it was first noticed between the ages of 4 to 6. Twenty were in patients between the ages of 16 to 49 and five between 54 to 82. Predominantly a tumor of the younger age groups and usually discovered late in most because of paucity of symptoms, it is generally slowly growing and benign. Seven have been reported as malignant, with demonstrable metastases in five. Death occurred from metastasis as late as nine years later. In all thirteen of those under the age of 15 there was macro-

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Read at annual meeting, American Urological Association, Chicago, Ill., May 21, 1951.

[1] Melicow, M. M., Robinson, J. N., Ivers, W. and Rainsford, L. K.: J. Urol., 62: 672, 1949.

[2] Warren, S. and Olshausen, K. W.: Am. J. Path., 19: 307, 1943.

No doubt there are cases which are diagnosed as other than interstitial cell tumor which may well be classified as such. Snellman's[12] which is classified under hyperplasia has the attributes of tumor as well. Teilum's[4] three cases of androblastoma, particularly his first, might be so listed. Lewis and Stockard's[13] case which they prefer to call a probable Sertoli cell tumor is in all probability similar to many of the accepted cases in the tabulation above and only future investigative work including hormonal studies and differential tissue staining will bring about a solution of this dilemma.

CASE REPORTS

Case 1. A man, aged 26, first seen by a general surgeon on November 20, 1947, complained of bilateral breast enlargement noticed for about 2 weeks. He was given 1 mg. stilbesterol daily for 2 weeks, at which time there was an apparent increase in the size of both breasts. Examination then revealed a small right hydrocele with a palpable hard area in the left testicle. Referred to the author, the left testicle was found to be unenlarged, but there was a hard, circumscribed area at the lower portion of it. Aspiration of the right hydrocele and careful palpation of the right testicle revealed no abnormality. Chest roentgenogram was negative. Urine gonadotropin prolan A was reported as less than 16 mouse units (normal 0 to 50). A left orchiectomy was performed on January 12, 1948.

Pathologist's (Dr. George Maner) report: Testicle measures 6 by 3½ by 3 cm. The tunica albuginea is intact The cut surface shows well circumscribed, apapparently encapsulated tumor measuring 26 mm. in maximum diameter in the lower pole of the testes. The tumor bulges and is predominantly brown and partly yellowish-gray. Microscopic: Section shows the tumor to be made up of imperfectly formed alveolar masses and tubular strands of large, pale, rounded or polyhedral-shaped cells resembling the interstitial cells of the testis. The cells comprising the tumor are slightly larger than the usual interstitial cell and possess finely granular opaque cytoplasm. In some areas the cytoplasm is lightly speckled with a brown staining material. On the margin of the tumor there are found groups of interstitial cells which appear to be beginning neoplastic. No mitotic figures are found. In the central portion of the tumor the cells are foamy-appearing. Histologically this tumor appears to be a hypernephroid type of interstitial cell tumor. Diagnosis: Interstitial cell tumor, hypernephroid type (fig. 1, *A* and *B*).

A slide was sent to the Armed Forces Institute of Pathology where the diagnosis was accepted. Through delay in establishing the diagnosis and through ignorance of the potentialities of the tumor, immediately postoperatively regional radiation was given. When the diagnosis was established, a belated investigation of endocrine factors was made. The patient stated that his libido had been greatly increased and that his abnormal sexual desires could not be palliated by regular intercourse. On December 8, 1949, a differential hormone assay of the urine was reported as follows: assay for 24 hour specimen of urine, total estrogens 4.7 micrograms (normal 5 to 15); total androgens 12.3 mg.

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[12] Snellman, B.: Am. J. Cancer, 35: 258-263, 1939.
[13] Lewis, L. C. and Stockard, C. G.: J. Urol., 64: 767, 1950.

in individuals of the same and different age group as well as in hyperplasia and tumor formation. In malignant tumors, with less cellular differentiation, the lipid content is usually much less. It follows that endocrine activity is not proportionate to the actual number of interstitial cells present, thus providing for a dissimilarity of changes among individuals.

The steroid nucleus recurs with minor changes in the various sex hormones, in their excretion forms, and in other adrenal cortical hormones. The similarity in chemical structure between the various hormones of the gonads and adrenals must account for the production of fairly similar phenomena by these different hormones. For instance, the androgens may have a great similarity to progesterone in both humans and in experimental animals. Testosterone has also been demonstrated to produce estrogen-like effects in a number of experimental animals. Ovarian tumors which are ordinarily feminizing may masculinize.*

The suspicion must be raised that more than one type of hormone may be produced from cells which are known to produce predominantly another type. For instance, granulosa cell tumors, thecoma and luteoma arising from the ovary produce clinical characteristics chiefly estrogenic in effect such as precocious feminization in childhood, but in rare cases hirsutism and other manifestations of virilism. By analogy, interstitial cell tumor of the testicle may perform in an opposite direction.

REPORTED CASES

To tabulate all the cases of any pathological entity is well nigh impossible because the literature is only incompletely available to any one author. Furthermore, this difficulty is increased when plausible differences of interpretation of microscopic studies of abnormal tissue exists such as in testicular tumors. The earlier reported cases deny the opportunity of re-examination of original slides or of the printed reproductions to those who follow.

The tabulation which is given by the present author is presented within these limitations (table 1). It is derived from the publications of Warren and Olshausen,[2] Nation, Edmondson and Hammack[5] and Melicow et al.[1] with deletions of those cases listed as not likely to be interstitial cell tumors. Among these are the cases of Slanina, Stappato and Villata. We have made additions of cases which have not been listed by any of the above authorities which nevertheless appear to be cases of interstitial cell tumor, namely, the cases of the following: Sutherland,[6] Reiners and Horn (2 cases),[7] Fraser,[8] Gharpure,[9] James and Shupe and[10] Scully and Parham.[11]

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* Hoffman, Jacob: "Female Endocrinology." Philadelphia and London: W. B. Saunders Co., 1945, page 47. "In view of close chemical relationship existing between the ovarian and testicular hormones, it is not surprising that perversion of ovarian function, as seen in certain ovarian neoplasms . . . may result in the production of substances possessing androgenic activity."

[5] Nation, E. F., Edmondson, H. A. and Hammack, R. W.: Arch. Surg., **48**: 415–422, 1944.

[6] Sutherland, D. M.: Brit. J. Surg., **20**: 343, 1944.

[7] Reiners, C. R. and Horn, R. C. Jr.: Am. J. Clin. Path., **19**: 1039–1047, 1949.

[8] Fraser, K. B.: Australian & New Zealand J. Surg., **19**: 48, 1949.

[9] Gharpure, V. V.: J. Path. & Bact. (Gr. Brit. and Ireland) **62**: 113–115, 1950.

[10] James, D. C. and Shupe, R. D.: J. Urol., **63**: 718–723, 1950.

[11] Scully, E. R. and Parham, A. R.: Arch. Path., **46**: 229, 1948.

24. Warren & Olshausen	1943	30			Benign		Well 3 years p.o.
25. Bonser & Hawksley #1	1943	19			Benign		
26. Bonser & Hawksley #2	1943	31			Benign	-	Well 6 months p.o.
27. Sharnoff & Lisa	1943	67			Malignant		
28. Rezek	1943	10			Benign	Macrogenitosomia	To be reported by Dr. Rezek (per Melicow)
29. Neeve & Marsh	1944	48		5 cm	Benign		
30. Nation, Edmondson & Hammack #1	1944	34			Benign	None	
31. Nation, Edmondson & Hammack #2	1944	30	28		Benign	Gynecomastia, bilateral	No regression after 3 years
32. Nation, Edmondson & Hammack #3	1944	82			Malignant	None	Died 1½ years p.o.
33. Anderson	1946	6			Benign	Macrogenitosomia	Regression of main symptoms
34. Scully & Parham	1948	55		8 cm	Benign	None	Died 10 years 7 months later; autopsy: no metastasis
35. Melicow et al	1949	5½	5		Benign	Macrogenitosomia	No regression 6 months
36. Reiners & Horn	1949	34		2.5 cm	Benign	Increased libido	Increased gonadotropins
37. Reiners & Horn	1949	54		2 x 1 x 1.3 cm	Benign	None	
38. Fraser	1949	4½	4	"rather bigger"	Benign	Macrogenitosomia	Regression of sexual precocity
39. Gharpure	1950	45		8.5 x 8 x 7.5 cm	Malignant	None	Metastasis to skull and lungs and local recurrence
40. James & Shupe	1950	14	9	7 x 5 x 3 cm	Benign	Macrogenitosomia	No regression 6 months

Questionable Cases Not Reported as Interstitial Cell Tumor

Snellman	1939	67			Benign		Reported as hyperplasia but entire testicle infiltrated with IC
Teilum	1946	53		6 x 4 x 3 cm	Benign	Gynecomastia, bilateral	Reported as androblastoma, homologous to arrhenoblastoma
Lewis & Stockard	1950	68		6.5 cm	Benign	Gynecomastia, bilateral	Reported as feminizing tumor probably from Sertoli cells

TABLE 1. *Interstitial cell tumors of the testicle reported in the literature*

AUTHOR	Year	Age	Age of Onset	Size	CHARACTER	ENDOCRINE CHANGES	REMARKS
1. Sacchi	1895	9	5	289 g.	Benign	Macrogenitosomia	Orchidectomy
2. Chevassu	1906	27		Egg	Benign	None	Orchidectomy
3. Kaufmann	1908	30		210 g. 140 g.	Benign	None	Bilateral
4. Kaufmann	1908	34		140 g.	Benign	None	Brother of case above
5. Masson & Sencert	1923	62			Malignant	None	Metastasis, died 52 months later
6. De Josselin de Jong	1926	42		Child's head	Malignant	None	Intra-abdominal metastasis, died
7. Monaschkin	1926	30		9 cm., 210 g.	Benign	Gynecomastia, bilateral	Regression left breast p.o.
8. Rowlands & Nicholson	1929	9	6	5 × size of opposite		Macrogenitosomia	No regression p.o.
9. Pitrollfy-Sazbo	1930	40				See remarks	Internal masculine pseudohermaphrodite
10. Pana	1931	16		28 g.	Benign	None	Opposite was inguinal
11. Sutherland	1933	11		4 x 3 in.	Benign	Macrogenitosomia	
12. Stewart, Bell & Roehlke	1936	5	4	210 g.	Benign	Macrogenitosomia	Regression only of hirsutism
13. Rigoletti	1936	20			Benign	None	
14. Jemerin	1937	35			Benign		
15. Budd	1937	42	41	2 x 2 x 2.5 cm	Benign	Gynecomastia, bilateral	Regression p.o.
16. Hunt & Budd	1939						
17. Braun	1939	45			Benign		Died from CA of stomach
18. Fialho	1941	44					
19. Somerford	1941	11	5	size of orange	Benign	Macrogenitosomia	No regression after 18 months
20. Huffman	1941	6	4	5 cm		Gynecomastia, macrogenitosomia	Some regression genitalia
21. Masson	1941	9	4	130 g	Malignant	Macrogenitosomia	Metastasis to liver
22. Masson & Venning	1942	32			Malignant		
23. Werner et al	1942	6	5				

Case 2. A man, aged 50, consulted an associate for hydrocele of the left testicle on March 30, 1938, and stated that he had noticed a lump in the left testicle six years prior to that time. Straw colored fluid (220 cc) was aspirated from the hydrocele. Because of induration of the testicle tumor was considered. Surgery for the hydrocele was performed on April 21, 1938, at which time the appearance of the testicle militated against the diagnosis of tumor. Over a period of several years he had been seen by doctors for complaints considered to be on a neurotic basis. In 1941, the administration of 120 mg. of testosterone propionate in divided doses resulted in moderate relief of his nervousness. In 1943 he was treated for overweight and nervousness. In 1944 he was unable to work because of mental depression. In 1946 another urologist noted the enlargement of the left testicle but ascribed it to the hydrocele operation.

He was first seen by the author on May 26, 1947, at which time the left testicle was found to be only questionably larger but quite firm. Again this was attributed to the hydrocelectomy. On June 30, 1948, he returned because of nocturia at which time the testicle was found to be as on the previous examination. The patient had recently been divorced. This and his inability to obtain employment increased his nervousness. On August 15, 1949, he was referred back by a general surgeon who suspected a tumor of the left testicle. It appeared approximately the same size as that on the right, but it was uniformly hard but probably unchanged from previous examinations. It is to be noted that the first urologist who performed the hydrocelectomy had suspected a tumor preoperatively but decided against it at the time of the hydrocelectomy. In view of this orchiectomy was performed with reluctance on August 23, 1949.

Pathologist's (Dr. Anthony Camero) report: The testicle measures 6 by 4 by 4 cm. The tunica vaginalis is firmly adherent to the tunica albuginea by fibrous adhesions. In the testis proper near one end is a well circumscribed, encapsulated tumor mass measuring 4 by 3½ by 3 cm. The cut surface of the tumor bulges, is predominantly dark red and shows much coarse yellowish speckling. The capsule around the tumor is intact, dense and fibrous. The tumor could be shelled out from the adjacent essentially normal testicular parenchyma. (Because of our previous experience the gross appearance made us strongly suspect the presence of interstitial cell tumor of the testicle.)

Microscopic examination of the two large representative sections of the testicular tumor noted, grossly shows it to be made up of numerous closely arranged supportive connective tissue stroma. The tumor cells have rather distinct cell margins. The cytoplasm is abundant and acidophilic. Many of the cells have vacuolated cytoplasm and some show fine granules. The nuclei are predominantly small and round. While some are hyperchromatic, there is no appreciable degree of pleomorphism. In places the nuclei are eccentric. There are scattered small deposits of finely granular brown pigment, presumably hemosiderin. There are also irregular areas of hemorrhage. Around the periphery there is a thick, fibrous partly hyalinized connective tissue capsule. A section of the adjacent testicular parenchyma shows no noteworthy histologic abnormalities. The gross and histologic appearances are consistent with a diagnosis of inter-

(normal 8 to 16); ganadotropins none (normal 0 to 25 international units). Liver function tests were within normal range. By January 4, 1949 the breasts had receded to normal. He was placed on estinyl estradiol .02 mg. daily for 1 month with no relief of his increased libido. When last seen October 8, 1949 the breasts were entirely normal, his sexual complaint remained the same, and he contemplated marriage as a solution.

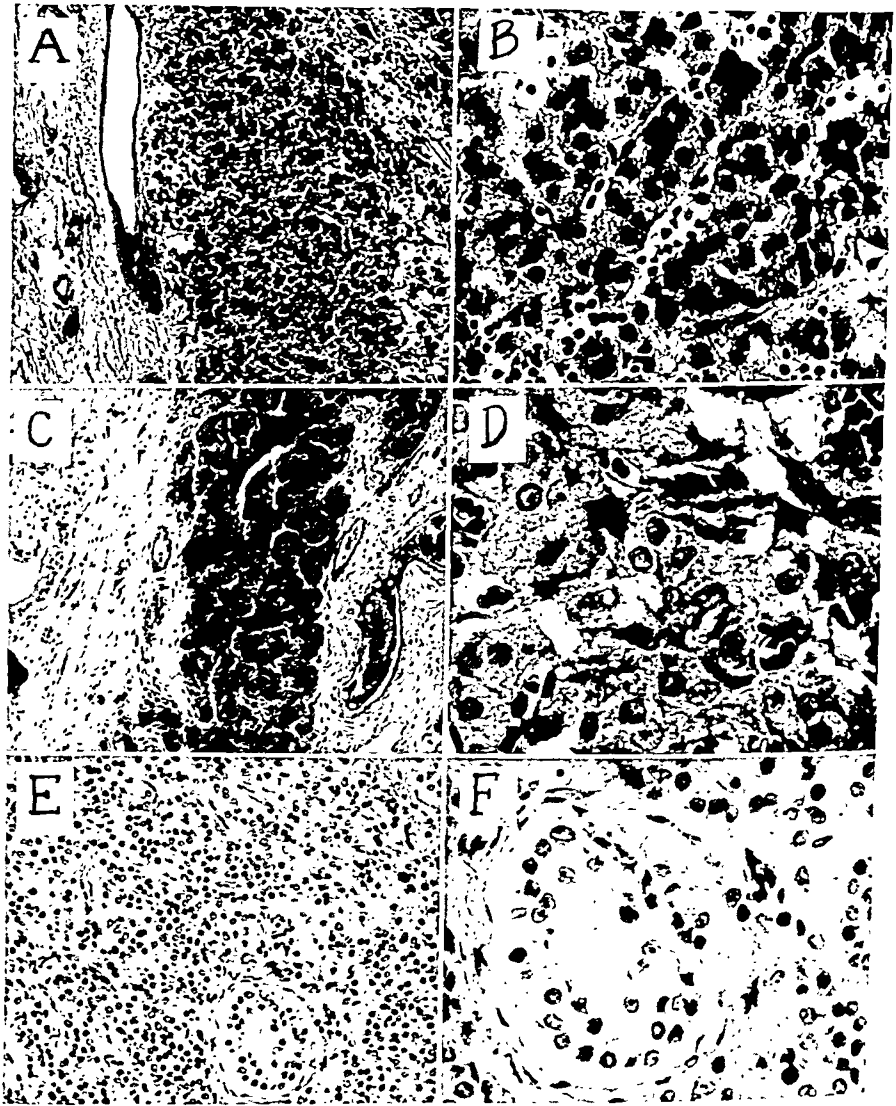

FIG. 1. *A* and *B*, case 1. *A*, interstitial cell tumor of testicle, ×60. *B*, interstitial cell tumor of testicle, ×350.

C and *D*, case 2. *C*, interstitial cell tumor of testicle, ×60. *D*, interstitial cell tumor of testicle, ×350.

E and *F*, case 3. *E*, interstitial cell tumor of testicle, ×110. *F*, interstitial cell tumor of testicle, ×275.

In the prepuberal age period striking changes in the sexual appearance have been uniformly present.

Endocrine changes, when present in the adult, are usually limited to gynecomastia.

Interstitial cell tumor is most likely to be confused with arrhenoblastoma of the testicle (the androblastoma of Teilum), adrenal cortex rest tumor, and Sertoli cell tumor.

Confusion with probable Sertoli cell tumor in those patients with gynecomastia offers a problem difficult of solution and must await future investigation involving differential staining of tissues and more complete studies of hormone excretion and hormone content of tumor tissue.

All interstitial cell tumors possess potentialities of endocrine activity.

The intracellular lipids in these tumors are considered intimately associated with endocrine activity and the hormone involved is presumed to be androgen.

The factors which may be responsible for the variable endocrine manifestations of interstitial cell tumors is discussed. They are: 1) the interaction of the hormones of the gonads, adrenal and pituitary; 2) genetic differences which may exist in the individual; 3) a variation in the amount of intracellular lipids present; 4) the close chemical and biological relationships of the various hormones produced from the gonads and adrenal glands which permit these ordinarily different hormones to act similarly on occasion; and 5) the possibility that more than one hormone is produced by the tumor.

The multiple influences which bring about gynecomastia are stressed and discussed.

Forty cases are gleaned from the literature after elimination of the more questionable ones and the addition of unlisted ones to tabulations previously published.

It is believed that certain cases listed under hyperplasia, androblastoma, adrenal rest tumor and Sertoli cell tumor may well be cases of interstitial cell tumor.

Three additional cases are reported, all in adults, in one of whom gynecomastia existed, bringing the total to 43.

It is finally concluded from study of the literature that the diagnosis of an interstitial cell tumor of the testicle requires investigation to a greater extent than has heretofore been pursued in most cases reported including our own. It is suggested that whenever possible in those patients suspected of having a tumor of the testicle that preoperative studies be made for excretion of estrogens, androgens, 17-ketosteroids, gonadotropins and such intermediary products as pregnandiol.

stitial cell tumor. Diagnosis: Interstitial cell tumor of left testicle (fig. 1, *C* and *D*).

A slide was sent to the Armed Forces Institute of Pathology where the diagnosis of interstitial cell tumor was given. The patient was last seen April 1951 at which time an effort was made to further elaborate on any further possible endocrine symptoms. Patient had just remarried and the marriage had been annulled. Despite his marital failures patient denied having any sexual difficulties. At no time had the patient any enlargement of the breasts.

Case 3. (Reported through courtesy of Dr. Richard E. Peterfy who was in attendance on this patient.) The patient was first seen by Dr. Peterfy November 28, 1948 because of a small nodule in the left testis noticed while drying himself following a bath. Physical examination was normal. The right testis was normal. There was a small, hard nodule found in the left testis about 1 by 1 cm. Routine laboratory work performed was normal. The testicle did not appear to be enlarged. Orchiectomy was performed shortly afterwards.

Pathologist's (Dr. Nathan Friedman) report: The testicle is 5 cm. in the greatest diameter; bulging from the surface opposite the epididymis is a 0.5 cm. thin-walled nodule resembling a cyst. Underneath this area is a 3 cm. irregular mass composed of lobulations of reddish tan and light grayish yellow tissue. In other areas there is definite fibrous trabeculation and streaking and in others very prominent bright golden yellow foci up to 2 by 3 mm. The remainder of the testis does not appear abnormal.

Microscopic examination: Sections of the testicular tumor reveal one composed of cords and nests of polyhedral cells with ample eosinophilic cytoplasm. The nuclei are for the most part round and regular. There is considerable fibrosis with areas of hyalinization of both previous tumor and testicular parenchyma. The testicular tubules themselves show a moderate degree of suppression of spermatogenesis but no striking atrophy other than in the scarred areas. There are also deposits of pigment presumably derived from blood. Sections of the cord and epididymis show no essential abnormalities. Diagnosis: Interstitial cell tumor, testis (fig. 1, *E* and *F*).

SUMMARY AND CONCLUSIONS

Interstitial cell tumors of the testicle are derived from the cells of Leydig and may develop as a result of hyperplasia of these cells.

Hyperplasia is usually found in conditions resulting in a decrease of spermatogenesis.

It is often difficult to distinguish between advanced hyperplasia and tumor formation.

The tumors are generally yellowish or brownish in appearance and frequently nodular as though encapsulated.

It is more commonly a tumor of the younger age groups.

It is generally benign although seven cases have been reported as malignant.

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RECOGNITION OF PHLEBOTHROMBOSIS AND PREVENTION OF PULMONARY EMBOLISM IN UROLOGIC PATIENTS*

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Judging by the accumulated literature, urologists have shown very little interest in the subject of this paper. Practically all of the valiant efforts to control pulmonary embolism and the antecedent phlebothrombosis have emanated from general surgeons and internists, many of whom have been greatly concerned about the gravity of this problem. Only two years ago an editorial[1] concluded with the warning, "the challenge of pulmonary embolism still exists in major form."

In 1940, one of us[2] (Culp) reviewed the records of all the cases encountered at the Brady Urological Institute, Baltimore, during the preceding 20 years and found that 6.6 per cent of the postoperative deaths had been caused by large pulmonary emboli, demonstrated at necropsy. Colby[3] became concerned enough about thrombo-embolism that he resorted to prophylactic ligation of the superficial femoral veins before prostatectomy. In 1946, 42 per cent of the deaths on the urologic service at the Henry Ford Hospital were due to pulmonary embolism (fig. 1). The incidence of this complication may have been much lower in many centers, but it seems fantastic to assume that pulmonary emboli have been a serious threat to urologic patients only in Baltimore, Boston and Detroit.

It is generally agreed that in many cases pulmonary infarction has been diagnosed erroneously as pneumonia, atelectasis or cardiac disease. Even postmortem data were misleading until the true significance of thrombo-embolism was appreciated fully. Flagrant clinical misinterpretations still exist today. Comparison of antemortem diagnoses and postmortem findings in cases of sudden death soon reveals the thinking habits of most clinicians. Coronary occlusion always has been and probably always will be a popular and convenient pigeon hole.

The earlier study[2] revealed a few patients with unsuspected pulmonary infarcts which were discovered at necropsy and which contributed to the death of those individuals even though they did not cause sudden death. There is every reason to believe that many pulmonary emboli continue to elude diagnosticians.

During recent years we have tried to learn through informal personal inquiries what other urologists believe regarding thrombo-embolism. Some insisted that they no longer "see" pulmonary embolism and attributed their good

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[1] Editorial: New Eng. J. Med., 241: 719–720, 1949.

[2] Culp, O. S.: Bull. Johns Hopkins Hosp., 67: 1–24, 1940.

[3] Colby, F. H.: J. Urol., 59: 920–924, 1948.

ADDENDUM

Since preparation of the foregoing paper, the following cases[14, 15, 16, 17] of interstitial cell tumors of the testicle have come to our attention.

AUTHOR	Year	Age	Age of Onset	Size	CHARACTER	ENDOCRINE CHANGES	REMARKS
41. Lewis	1949	37	35		Benign	None	Well 12 years postoperatively
42. Lewis	1949	25	23		Benign	None	Radical orchiectomy in error
43. Garvey & Daniel	1951	19	14	R—7.5 x 4 cm. L—6x 4 x 3.5 cm.	Benign, bilat.	None except lack of interest in opposite sex	Considered similar to Snellman's case
44. Grabstald, et al.	1951	32		1 cm	Benign	Bilateral gynecomastia; loss of libido	Associated with xanthoma; no orchiectomy; tumor only removed.
45. Christeson & Nettleship	1952	76		3 x 5 cm.	Benign	Bilateral gynecomastia and loss of libido	Regression of gynecomastia preoperatively

947 W. 8th St., Los Angeles 17, Calif.

[14] Lewis, L. G.: Advances in Surgery, **2**: 442, 1949.
[15] Garvey, F. K. and Daniel, T. B.: J. Urol., **66**: 713, 1951.
[16] Grabstald, H., Haines, J. S. and Morrow, A. G.: J. Urol., **66**: 708, 1951.
[17] Christeson, W. W. and Nettleship, A.: J. Urol., **67**: 350, 1952.

Sixty-five per cent of all urologic patients who died during the 7 years covered by this study had necropsy. Nine patients had massive pulmonary emboli. A tenth patient died in uremia because thrombosis extended from the lower extremities along the vena cava to include the pedicle of her only kidney.

All deaths during this period that lacked postmortem studies have been reviewed in minute detail. Seven of these patients *probably* died of pulmonary embolism and have been added, as shown in figure 2.

Excluded from our analyses were 5 additional patients with pulmonary embolic phenomena that had no bearing on the basic problem which we hope to correct. They had minute incidental infarcts discovered at necropsy, embolus of tumor tissue, or terminal care for generalized carcinomatosis.

Confirmed skeptics may scoff at concerted efforts to eliminate such a small number of fatalities. Even the most disastrous year included the loss of only 5 patients. We insist that the death of any relatively healthy individual because of pulmonary embolism is usually a reflection on the alertness, attentiveness, diagnostic acumen and clinical judgment of the attending staff. Saving only a small group of patients must be accepted as a worthwhile project.

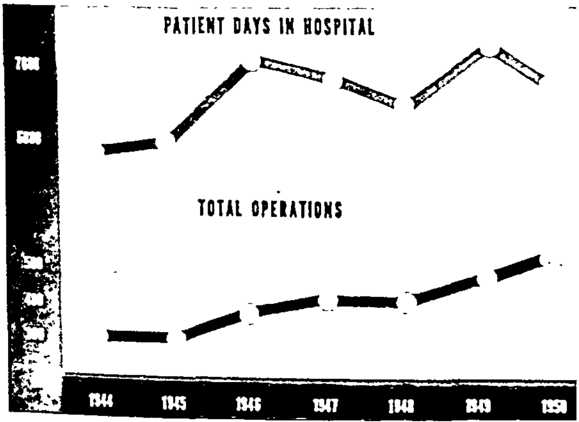

FIG. 3. Growth of urologic division during seven years.

No doubt any enthusiasm about our results should be tempered by the fact that the urologic service is not a huge one. Nevertheless it averaged 7,000 in-patient days and 500 operations during each of the last two years (fig. 3). Fatal pulmonary embolism was avoided despite continued growth of the division.

Although two and a half years have elapsed since our last large fatal embolus, patients have continued to have small infarcts with recovery (fig. 4). In fact the total number of all pulmonary emboli (fatal plus nonfatal) during each of these 7 years has fluctuated very little. However, from 1944 through 1947, most emboli were disastrous. Additional nonfatal infarcts may have been unrecognized during that period because especially diligent efforts to avoid overlooking any such lesions have been confined to the last 3 years. The higher incidence of infarction with recovery beginning in 1948 may be simply an index of improved diagnostic efficiency but it is conceivable that therapeutic measures employed fortune to early ambulation. We suspect that "recognize" would be more correct. Early ambulation has reduced the incidence of thrombosis and embolism but it has failed to eradicate the disease.

Other confreres admitted that they lose a patient occasionally but insisted that fatal pulmonary emboli are too rare to justify any elaborate prophylactic measures. We find it very difficult to be blasé about any untimely death that might have been prevented and cannot be reconciled to such rationalization.

Still other acquaintances agreed that thrombo-embolism continues to be a serious problem but feared that most of these misfortunes are inevitable. Inasmuch as thirty-one months have now elapsed (April 1951) since anyone died of pulmonary embolism on the urologic service at the Henry Ford Hospital, in contrast to the alarming frequency of this cause of death in 1946 (fig. 1), we hope that at least a few defeatists will find this fact grounds for justifiable optimism.

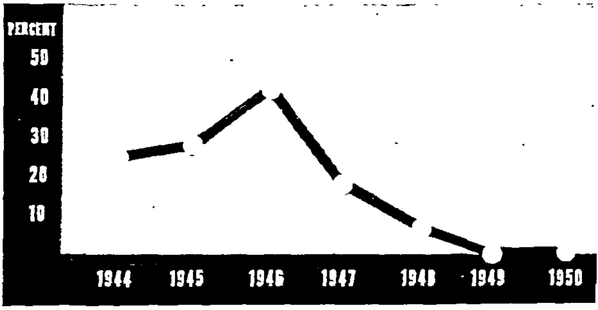

Fig. 1. Percentage of all deaths on urologic service due to thrombo-embolism

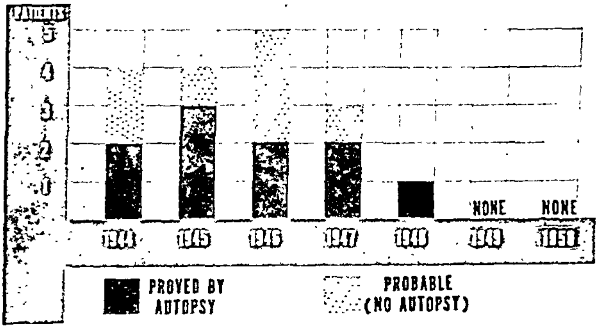

Fig. 2. Total number of patients with fatal pulmonary embolism.

CURRENT REVIEW

This study has been confined to the patients seen in the last 7 years to insure inclusion of only the most accurate clinical data and to cover the period of authentic early ambulation. Seventy-five per cent of the patients in whom thrombo-embolism developed during these years had been out of bed during the first 24 hours after operation. Although early ambulation was pioneered at the Henry Ford Hospital, it is apparent from figure 2 that this innovation did not eliminate fatal pulmonary embolism.

period studied. In 1949 and 1950, when there were no deaths, the number of cases of recognized phlebothrombosis rose to 19 and 16, respectively. It seems preposterous to explain this solely as an increased incidence of the disease. Even if one allows for a reasonable number of clinical errors, the striking difference is compatible with improvements in diagnosis.

Sixty-six patients with thrombo-embolism have been included in this study (table 1). Analysis of the fatal and nonfatal groups further emphasizes the danger of unrecognized thrombosis. Of the 49 patients who recovered, 94 per cent had been found to have phlebothrombosis in one of the lower extremities. Emboli in the other 3 cases may have originated in the operative region. In approximately 70 per cent of the cases the thrombosis was diagnosed early enough to prevent the patients' having even small pulmonary infarcts. This percentage is still higher if only more recent cases are considered.

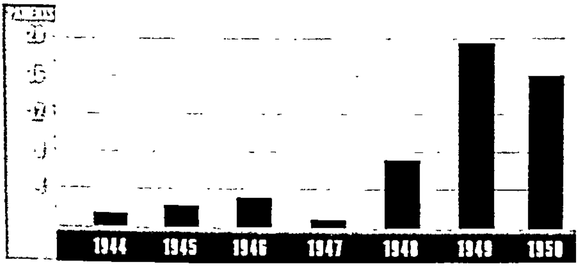

FIG. 6. Phlebothrombosis in the lower extremities recognized clinically.

TABLE 1. *General summary*

CLINICAL DATA	RECOVERED		FATAL		TOTAL
Number of patients	49		17		66
Postoperative	44		15		59
No operation		5		2	7
Thrombosis only	30	4	1*		35
Pulmonary embolus	14	1	14	2	31
Phlebothrombosis recognized	41	5	3		49
Embolism but legs remained negative	3				3
Phlebothrombosis not suspected			12	2	14

* Died from extension of thrombus—no embolus.

In 14 of the 17 fatalities, phlebothrombosis had never been suspected until the patients died of massive embolism. Review of the deaths from pulmonary emboli at the Brady Urological Institute[2] showed that thrombosis in the legs was recognized clinically in only 18 per cent of the cases proved by necropsy. Exactly the same percentage prevailed in the present smaller series.

The 59 patients with postoperative thrombo-embolism had a great variety of operations (table 2). These figures fail to justify any conclusions about the relative dangers of various types of surgery. Suffice it to say, thrombo-embolism followed suprapubic, perineal and even transurethral prostatic operations and, no doubt, can occur after any procedure on any part of the genito-urinary tract.

during these 3 years may have controlled the size of some emboli that otherwise might have been fatal.

Most pathologists agree that the lower extremities are the most common source of emboli large enough to cause sudden death. On the other hand, small emboli that produce nonfatal pulmonary infarcts may originate in pelvic venous plexuses or at any operative site.

Since the pathogenesis of most phlebothrombosis remains obscure, we have become reconciled to inevitable thrombosis. None of the so-called prophylactic measures available to date has been practical or entirely reliable. Early recognition of phlebothrombosis in the lower extremities seems to be the one hope of preventing serious pulmonary sequelae.

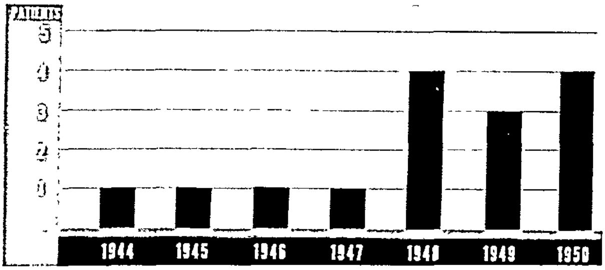

FIG. 4. Number of urologic patients who recovered from pulmonary infarction.

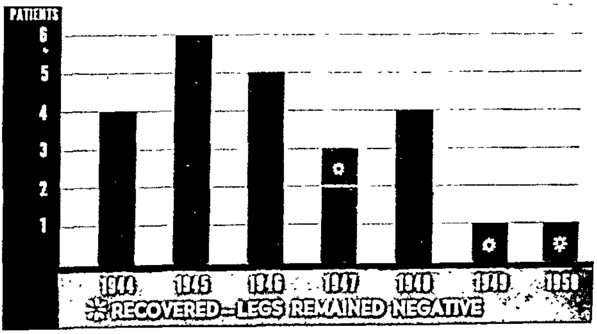

FIG. 5. Phlebothrombosis that was not suspected until patients had pulmonary emboli.

It is generally agreed that pulmonary complications cannot be averted as long as thrombosis in the legs escapes clinical detection. As shown in figure 5, the early years covered by this study had the largest number of pulmonary emboli before phlebothrombosis was even suspected. This was also the period of highest mortality (fig. 1). During the past two years when no one died of pulmonary embolism, only 2 patients had emboli prior to the diagnosis of thrombosis. Both of these recovered and their legs remained normal. One of us (Barron)[4] has discovered that cases of this type will not exceed 7 per cent of all cases of pulmonary embolism.

The importance of proper appraisal of the legs is emphasized further by figure 6. Phlebothrombosis was diagnosed rarely during the early years of the

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[4] Barron, James: Indust. Med. & Surg., 18: 422–425, 1949.

We are convinced that fatal pulmonary embolism has been avoided for two and a half years simply because most, if not all, phlebothrombosis in the lower extremities was recognized early enough during this period to be treated properly.

RECOGNITION OF PHLEBOTHROMBOSIS

In 1934, Homans[5] pointed out that "deep quiet thrombosis" in the calf veins precedes the more obvious changes in the leg and, if carefully searched for, it can be detected before there is any conspicuous edema, fever or other manifestations of thrombo-embolism. Similar observations were made by Denecke,[6] Rössle,[7] Frykholm,[8] Bauer,[9] and Hunter and co-workers.[10]

Our clinical experiences also confirm this concept. Only 3 patients in recent years had pulmonary embolism without evidence of phlebothrombosis in the legs. This is in direct contrast to the claim by Ochsner and his associates,[11] that in only approximately 50 per cent of the cases of fatal pulmonary embolism are there recognizable signs and symptoms of phlebothrombosis.

We have based the diagnosis of phlebothrombosis on careful correlation of three cardinal observations: 1) fever, 2) apprehension and 3) tenderness in the leg.

Fever.—Most of the patients in this series had a temperature of 99 to 101F prior to clinical detection of thrombosis. The high incidence of postoperative infections of the urinary tract makes interpretation of low-grade fevers especially difficult in urologic patients. However, we have become extremely prone to suspect that phlebothrombosis is present when any postoperative temperature becomes stabilized only to be followed by a second elevation, irrespective of the degree of fever.

Figure 7 shows the high morning and afternoon temperatures of the only patient who died of pulmonary embolism during 1948. This Negro male, aged 60, was admitted in acute urinary retention due to benign prostatic hypertrophy. Suprapubic cystostomy was necessary when he failed to tolerate a catheter in the urethra. The fever subsided and a second-stage suprapubic prostatectomy was performed without difficulty. Again the temperature was approximating normal when it suddenly rose to 101F. The following morning he was found dead in bed. Necropsy showed a massive pulmonary embolus. The phlebothrombosis had not been recognized but its presence should have been suspected.

Fever alone is not the most significant finding in phlebothrombosis but it must be accepted as an important warning. The patient's pulse rate may parallel or even exceed the rise in temperature.

Apprehension.—We have been impressed by the fact that many of our patients suddenly became extremely apprehensive on or about the time their phlebo-

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[5] Homans, John: New Eng. J. Med., **211**: 993-996, 1934.

[6] Denecke, Kurt: Der Plantarschmerz als Frühsymptom einer beginnenden Thrombose der unteren Extremität. München. med. Wchnschr. **76** (pt. 2): 1912-1913, 1929.

[7] Rössle, R.: Arch. Anat. u. Physiol. **300**: 180-189, 1937.

[8] Frykholm, Ragnar: Surg., Gynec. & Obst. **71**: 307-312, 1940.

[9] Bauer, Gunnar: J.A.M.A., **131**: 196-203, 1946.

[10] Hunter, W. C., Sneeden, V. D., Robertson, T. D. and Snyder, G. A. C.: Arch. Int. Med. **69**: 1-17, 1941.

[11] Ochsner, Alton, Kay, J. H., DeCamp, P. T., Hutton, S. B. and Balla, G. A.: Ann. Surg. **131**: 652-670, 1950.

In fact, operation is no prerequisite. Seven patients had thrombosis or embolism without having had any type of operative procedure (table 1).

Duration of operation, types of anesthesia, variations in blood pressure, cardiac status and original diseases may have been contributing factors in isolated cases of thrombo-embolism but none of these could be incriminated with any consistency.[8]

Ages of the patients varied from 25 to 84 years (table 3), with the highest incidence of thrombo-embolism during the seventh decade. This was also true in the Johns Hopkins[2] series but during that study it was noted that the largest number of urologic patients *without* thrombo-embolism also fell into the same age group. Males predominated in the present series almost 3:1.

TABLE 2. *Fifty-nine cases of postoperative thrombo-embolism*

OPERATION	FATAL	RECOVERED	TOTAL
Suprapubic	10	14	24
Renal	2	13	15
Transurethral	2	7	9
Perineal	1	4	5
Ureteral		4	4
Scrotal		2	2

TABLE 3. *Ages of 66 victims of thrombo-embolism*

YEARS	FATAL	RECOVERED	TOTAL
25–26	1	1	2
30–39		4	4
40–49	2	8	10
50–59	3	12	15
60–69	7	15	22
70–79	4	8	12
84		1	1

TABLE 4. *Fifty-nine postoperative cases*

TIME AFTER OPERATION	RECOGNITION OF THROMBOSIS	TIME OF EMBOLISM
1st. week	26	11
2nd. week	15	4
3rd. week	2	9
Later	1	4

Phlebothrombosis occurred in each leg with equal frequency and emboli had no preference for either lung. Most of the thrombosis was discovered during the first and second postoperative weeks (table 4) while embolism was most frequent during the first and third weeks. Two patients had fatal pulmonary emboli less than twenty-four hours after operation. In all probability they had been subjected to operation in the presence of unrecognized phlebothrombosis. Unnecessary risks of this type must be deplored.

Similar pressure is applied along the medial aspect of the calf posterior to the tibia (fig. 9, *A*).

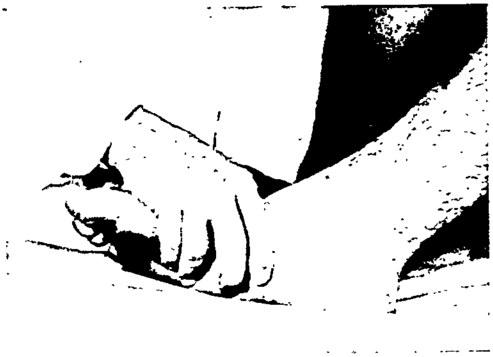

Fig. 8. Step 1 in examination of legs: palpation of plantar surface of foot.

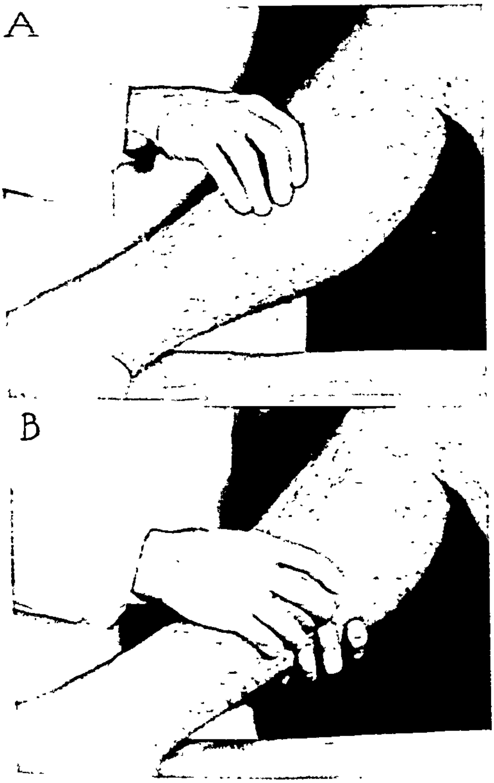

Fig. 9. *A*, step 2 in examination of legs: gentle but firm pressure applied to medial side of calf posterior to tibia. *B*, step 3 in examination of legs: compression of deep muscles of calf against posterior surface of tibia and fibula.

With the fingers slightly flexed, gentle but firm pressure is exerted to compress the deep muscles of the calf against the posterior surface of the tibia and fibula (fig. 9, *B*). This is the most common site of tenderness in the leg. Occasionally the tender thrombosed vein can be palpated in this region.

thrombosis was first recognized or just before pulmonary embolism developed. This is not to be confused with the customary anxiety which any surgical victim may have regarding the success of his particular operative procedure. Instead, we refer to individuals who seemed to be emotionally stable, yet they suddenly had morbid fear of impending danger, undue tenseness regarding their surroundings or an overwhelming desire to have constant professional vigilance. Gunnar Bauer[12] of Sweden has informed us that he has made similar observations.

Such changes in patient behavior can be measured only empirically and, therefore, may have no appeal to the calloused scientist. Interpretation obviously must depend on human understanding rather than the technical skill of the observer. The value of this clue will vary with the type of rapport that exists between patient and physician and not infrequently it will be interpreted best by interns or residents.

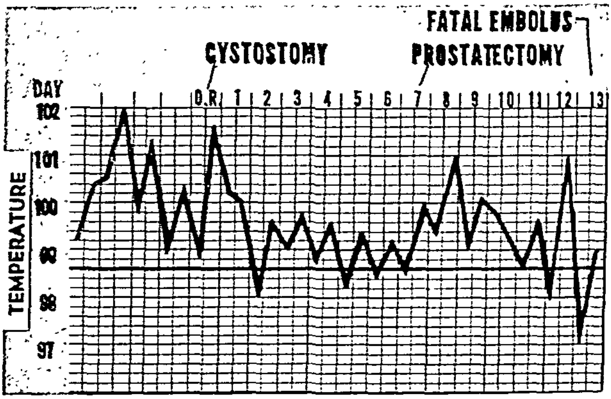

FIG. 7. Temperature curve of only patient who died of pulmonary embolism during 1948.

Apprehension per se cannot be attributed solely to threatened thrombo-embolism. We offer it only as another possible warning sign that should not be ignored.

Tenderness of the leg.—In 1949, one of us (Barron)[4] reported positive findings in the legs in 93 per cent of all cases of thrombo-embolism that had been under personal observation. Tenderness in the leg appears to be the most significant indication of early phlebothrombosis. The onset of obvious edema proves that the early stage has gone unrecognized and indicates extension to the popliteal or femoral vein. Every effort must be made, therefore, to detect thrombosis before it spreads to these vessels. We are convinced that this is possible once an examiner has attained reasonable proficiency in evaluating the condition of the lower extremities.

Our technique for examination of the legs is illustrated in figures 8 and 9. With the patient recumbent and knees partially flexed to relax the muscles, the plantar surface of each foot is palpated gently but firmly, as shown in figure 8. We encountered less than 3 per cent of tenderness in this region.

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[12] Bauer, Gunnar: Personal communication to the authors.

veins were ligated before major urologic operations were attempted. The data on 1 of these patients are summarized in figure 10. The temperature was elevated the day before phlebothrombosis was diagnosed and gradually returned to normal after ligation of the veins. The postprostatectomy convalescence was uneventful.

Forty patients were treated with heparin. This was given by the intermittent, intravenous method that has been used extensively in Sweden for several years.[13] It was administered four times daily for an average of ten days in doses of 25 to 125 mg.

All patients were confined to bed until the tenderness in the calf disappeared. During rest in bed, exercise of the legs is mandatory. All pain and tenderness in the lower extremities frequently disappeared within twenty-four hours after institution of heparin therapy. Such findings seldom persisted beyond the fourth day of treatment, providing the diagnosis was made reasonably early. As a rule, apprehension disappeared promptly and the temperature became normal within two to four days.

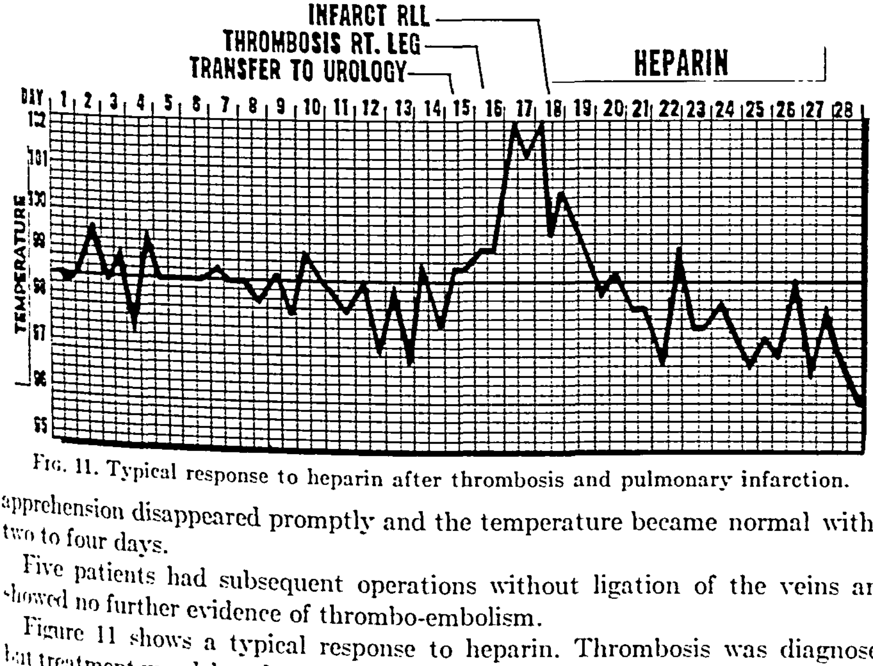

Fig. 11. Typical response to heparin after thrombosis and pulmonary infarction.

Five patients had subsequent operations without ligation of the veins and showed no further evidence of thrombo-embolism.

Figure 11 shows a typical response to heparin. Thrombosis was diagnosed but treatment was delayed and a small pulmonary infarct developed. This further stresses the importance of *prompt* therapy once phlebothrombosis has been suspected. The rapid reduction of the fever is to be noted.

Clotting times were not used as a therapeutic index except in patients with decreased renal function. With moderate increase in the concentration of nonprotein nitrogen or comparable decrease in excretion of phenolsulfonphthalein, the clotting time was determined before each 4 p.m. injection of heparin. When this clotting time was more than thirty minutes, the dose of heparin was reduced

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[13] Jorpes, J. E.: Heparin in the Treatment of Thrombosis; an Account of Its Chemistry, Physiology and Application in Medicine. Ed. 2. London: Oxford University Press, 1946, 260 pp.

Any developing tenderness in the regions mentioned cannot be ignored safely inasmuch as no one can predict the future course of events. Experience has shown that it is much better to err on the safe side and treat a few patients unnecessarily rather than delay therapy in an incipient case of bona fide thrombosis.

This type of examination has been used routinely and methodically on our urologic service during recent years only. To be truly effective, it is imperative that interns and residents be thoroughly indoctrinated. The examination should be made *at least twice daily* on every patient regardless of activity or operative status. Significant changes may occur within very few hours.

Despite expert interpretation of leg findings, a few patients may have pulmonary embolism without positive signs referable to the legs. Most of these, however, will have lesions that are small and nonfatal and that probably will originate in the pelvic venous plexuses or in the operative region. There were 3 such cases in our series.

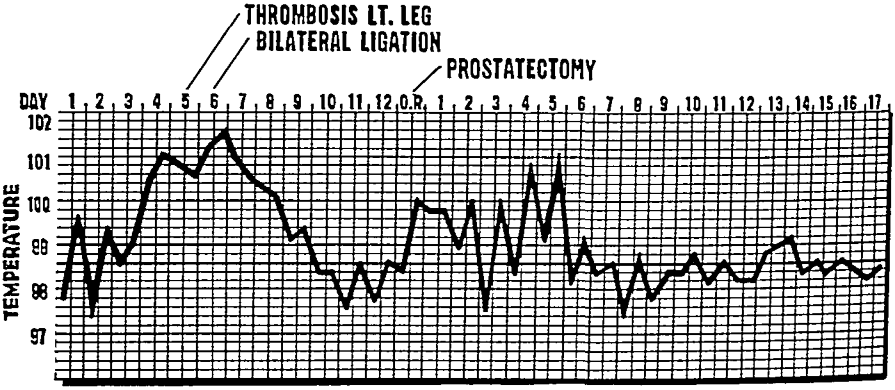

FIG. 10. Phlebothrombosis recognized before contemplated operation and treated with bilateral ligation of superficial femoral vein.

TREATMENT OF PHLEBOTHROMBOSIS

Much has been written about treatment of recognized phlebothrombosis. Most recent authors have tried to be champions of either anticoagulants or ligation of veins. Results to date would seem to indicate that no one method or drug is perfect. It is not within the scope of this presentation to argue the relative merits of the current schools of thought. We are convinced that both ligation and anticoagulants have intrinsic value and that the most rational therapeutic regimen will include the desirable features of both principles. We intend merely to summarize our experiences with this group of patients and outline the plan which we prefer to follow.

In 1945 and 1946, phlebothrombosis was diagnosed in 3 cases but no treatment was given. Opinions differed regarding the advisability of ligating the femoral veins. Two patients promptly died of pulmonary embolism. The third recovered without any emboli.

Ten patients had ligation of their superficial femoral veins. In 3 cases the

Three other patients (not included in table 5) had some increased bleeding while taking heparin after transurethral resection, suprapubic prostatectomy and nephrectomy, respectively, but it was insufficient to require cessation of therapy.

Figure 12 summarizes the data pertaining to the interesting exacerbation of phlebothrombosis that occurred despite a full course of heparin. The condition was recognized promptly and additional heparin prevented any embolic complications.

Three patients had nonfatal pulmonary infarcts after use of heparin had been discontinued (table 5). None of these had received a full ten-day course of the drug. In 2 cases the infarcts occurred after the patient went home. Both were readmitted to the hospital, treated for 10 days with heparin and had no further evidence of thrombo-embolism. The third patient who had received inadequate anticoagulant therapy had both superficial femoral veins ligated.

TABLE 5. *Forty patients treated with heparin*

	No complications: clinical cures (Average course of drug—10 days)	32
Complications	Excessive bleeding requiring cessation of treatment (Heparin given for 1, 2, 6 days respectively)	3
	Exacerbation of thrombosis without embolism after heparin was discontinued (Cured by second course of 10 days)	1
	Non-fatal pulmonary infarcts after heparin was stopped (Each had less than 10 days of Heparin)	3
	Fatal pulmonary embolus at home in bedfast patient (Vein ligation advised but declined)	1

Another patient had no operation, developed phlebothrombosis that was recognized without delay, and responded promptly to heparin therapy. She had been bedfast for 2 years with crippling arthritis and since she was destined to continue her nonambulatory status, ligation of veins was advised but was declined. She died of pulmonary embolism 6 weeks after leaving the hospital (table 5). This had actually been predicted and there is ample opportunity for philosophizing about the terminal event. The results in this case can hardly be misconstrued as a reflection on the heparin therapy.

As further evidence that the alleged hazards of treatment with heparin soon after operation are minimal, there were 22 cases in which administration of the drug was started during the first postoperative week with no subsequent hemorrhagic complications (table 6).

Pulmonary embolism followed in 1 of the 10 cases of bilateral ligation of superficial femoral veins. That individual recovered and the source of his embolus remained uncertain. Six of the 10 patients had some degree of persistent edema to 25 or 50 mg. or it was omitted. Otherwise, routine doses of the drug were given as long as there were no hemorrhagic complications.

Contrary to many popular phobias we consider patients who undergo operations on the urinary tract especially suitable for anticoagulant therapy. Danger of concealed hemorrhage is minimal. Most incisions are drained routinely and bleeding into the urinary tract manifests itself promptly. Reluctance to use anticoagulants soon after operation is unjustified. We have noted that heparin produces less bleeding in patients with thrombosis than it does in normal individuals.

Olwin, Papierniak and Merricks[14] gave heparin and dicumarol to 4 patients who underwent transurethral prostatic resection, to prevent occurrence or recurrence of thrombo-embolism. No undue bleeding was encountered and the desired prophylactic effect was obtained in each case.

During the time of this study we preferred heparin over dicumarol for two reasons: 1) the therapeutic effect is noted much sooner and 2) the anticoagulant action can be nullified promptly by the intravenous administration of an equal amount of protamine sulfate. In our experience, long-acting preparations of heparin have produced too much discomfort and have been too unpredictable in their action. It must be remembered that any anticoagulant is a potentially dangerous drug and commands the profound respect of clinicians.

Intermittent administration of heparin has been criticized in some circles because the anticoagulant effect fluctuates unless it is given continuously. Doses small enough to avoid any excessive anticoagulability immediately after injection have been ridiculed because of alleged ineffectiveness during the several hours that elapse between doses. This type of program has been branded as being unscientific and logically unsound. Whether such criticisms are justifiable or not, the intermittent administration of heparin seemed to give very favorable results in controlling phlebothrombosis in the 40 patients of our series who were treated in this manner.

Results.—Thirty-two of the 40 patients who underwent anticoagulant treatment received a full ten-day course of heparin, had no increased bleeding and showed no further evidence of thrombo-embolism (table 5).

In 3 cases, use of heparin had to be discontinued because of excessive bleeding. In 2 of these 3 cases, administration of the drug had been started 4 days after transurethral resection of the prostate but had to be stopped on the second day of administration. Both patients had prompt ligation of their superficial femoral veins. One of these 2 patients, however, had a small pulmonary embolus 21 days after ligation. He recovered completely after 10 days of treatment with heparin during which there was no recurrence of his hemorrhage. The second patient who was treated by ligation had no further trouble. The third victim of excessive bleeding had been started on treatment with heparin 26 days after nephrostomy. Treatment had to be stopped 6 days later, but all signs referable to the legs had already disappeared. He had no embolism and required no more treatment.

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[14] Olwin, J. H., Papierniak, F. B. and Merricks, J. W.: J. Urol., **63:** 303–308. 1950.

the following therapeutic plan for the effective management of anyone suspected of having early phlebothrombosis in a lower extremity:

A. Bilateral ligation of the superficial femoral veins is performed if 1) additional operations are contemplated, 2) bleeding is excessive, 3) renal impairment is severe and 4) ambulation is impossible.

B. Heparin for other patients is given intravenously by the following method: 1) Technique: A No. 22 or 24 needle is used; pressure is applied at the site of venipuncture for ten minutes. 2) Dosage: A dose of 50 mg. is given as soon as thrombosis is diagnosed. Then, for 5 days, 75 mg. is given at 12 noon and 4 p.m., and 125 mg. is given at 8 a.m. and 9 p.m. After 5 days the dose is usually reduced to 75 mg. 4 times daily. Smaller doses may be advisable in isolated cases. 3) Duration: Treatment is continued for a minimum of 10 days, and until the patient has become ambulatory and has normal findings with respect to the leg. 4) Clotting time: This is determined before the 4 p.m. dose is given if there is evidence of renal impairment. If the clotting time is more than 30 minutes, the dose is reduced or omitted.

TABLE 7. *Results obtained with the previously described plan on one urologic service at the Mayo Clinic August 7, 1950, to April 1, 1951*

OPERATIONS		COMPLICATIONS, CASES	
Site	No.*	Phlebothrombosis in leg	Pulmonary infarct
Kidney	93	1	
Ureter	26		
Bladder	32	1	1
Prostate	42	1	
Urethra	13		
Genitalia	27		

* 13 operations are included in more than one category (8 procedures on the bladder were associated with simultaneous ureteral transplantation, and 5 suprapubic prostatectomies were combined with cystolithotomy or diverticulectomy).

This regimen has been most satisfactory despite any conflict with the theoretical features of antiembolic therapy, but it can never be instituted at the most opportune time unless phlebothrombosis in the lower extremities is recognized early.

SUMMARY

Pulmonary embolism continues to be a major problem despite early ambulation and so-called prophylactic measures. In 1946, it was responsible for 42 per cent of all deaths on the urologic service of the Henry Ford Hospital. After concentration on the early recognition of phlebothrombosis in the lower extremities and on prompt institution of appropriate therapy, there have been no deaths from pulmonary embolism among urologic patients for thirty-one months.

Early diagnosis of the thrombosis has been based on proper evaluation of fear, apprehension, and tenderness of the legs.

and discomfort in the legs. We noted none of this in any of the patients who were treated adequately with heparin alone.

It is apparent that both heparin and ligation of veins can be used to good advantage in the treatment of phlebothrombosis but each has its shortcomings. Edema and concomitant discomfort after ligation can be ignored more easily by surgeons than by patients. Isolated hemorrhagic complications seem to be inevitable after any type of anticoagulant therapy.

Intermittent use of heparin can be very effective in controlling thromboembolism providing the patients can be made ambulatory and the treatment is adequate. The exacerbations in this series clearly demonstrate the importance of continuing administration of the drug until all evidence of thrombosis has disappeared. Ten days may not be long enough if the findings referable to the legs are still present and if fever has not disappeared.

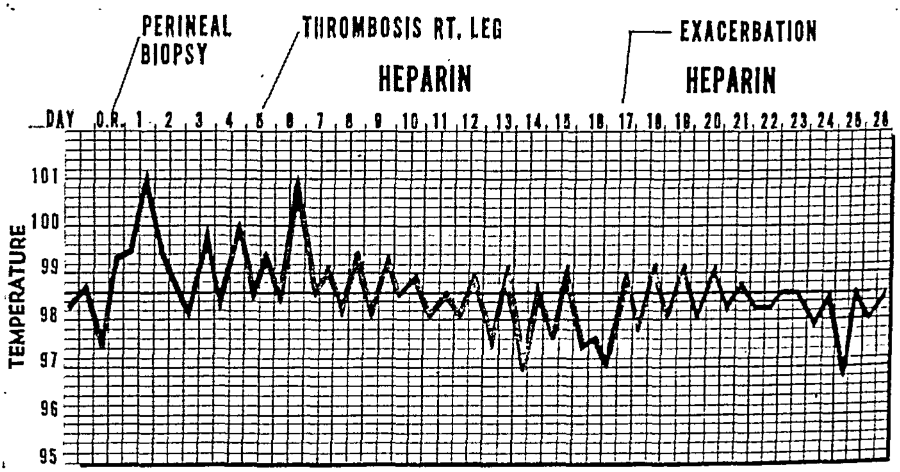

FIG. 12. Exacerbation of phlebothrombosis after routine heparin treatment, but complete recovery after second course of same drug.

TABLE 6. *Early postoperative administration of heparin without increased bleeding*

SITE OF OPERATION	POSTOPERATIVE DAY HEPARIN STARTED						
	I	II	III	IV	V	VI	VII
Prostate		2		2		1	1
Kidney	3		1		2	3	1
Bladder			1			1	
Ureter			1			1	1
Scrotum		1					

All of the embolic complications that occurred after treatment with heparin in this series can be attributed to attempted therapeutic short cuts, most of which were made early in our crusade. As one's experience in the diagnosis of early thrombosis and in the judicious administration of heparin increases, complications should become almost extinct.

From our own observations and the writings of other investigators, we evolved

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PROTECTIVE SHEATH FOR URINARY DRAINAGE TUBES

SIDNEY R. WEINBERG

From the Urological Service, Brooklyn VA Hospital, Brooklyn 9, N. Y.

Constant urinary drainage is acknowledged the most important factor in proper healing of cystotomy and nephrotomy wounds. At times an irrational or unconscious patient, by his movements or position, will occlude the lumen of the drainage tube. This condition frequently occurs to the rectal drainage tube, after ureterosigmoidostomy.

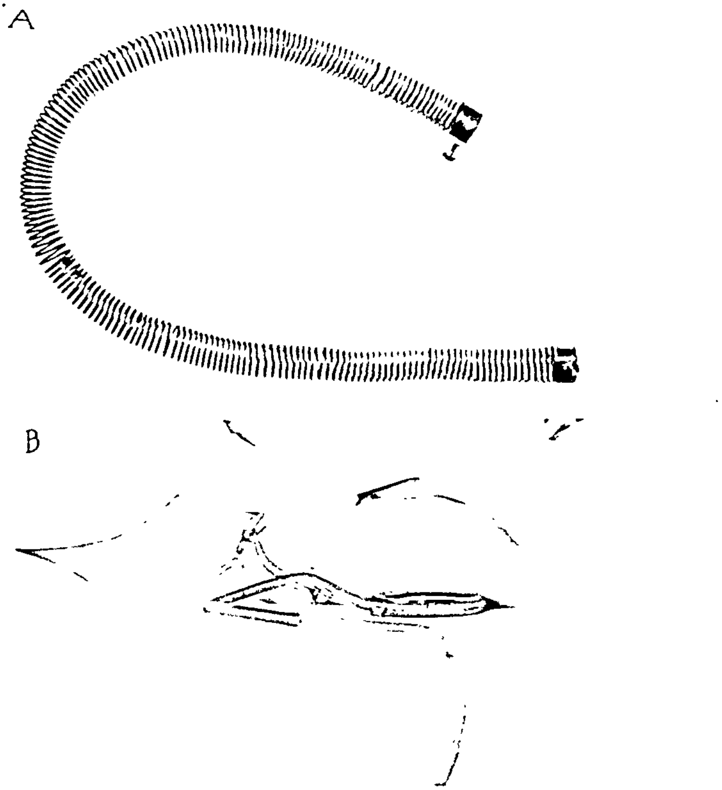

Fig. 1. *A*, protective sheath. *B*, protective sheath in use. Note pressure of limb and presence of irrigating fluid in glass adapter.

In order to forestall such an accident, a protective sheath was devised so that the weight of a patient's limb or pelvis would not crush the lumen of the drainage tube. This sheath is composed of a stainless steel spring coil, 24 inches long; the diameter of the coil is 5⁄8 inch; each and has a band 3⁄8 inch wide equipped with a set screw so that when the screw is tightened the bands at each end will secure the spring tightly to the shaft of the catheter and protect it from slipping. See figure 1. This sheath is being manufactured by C. R. Bard and Co., Summit, N. J.

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Treatment has consisted of intermittent, intravenous administration of heparin in most cases and of bilateral ligation of the superficial femoral veins in selected instances.

ADDENDUM

One of us (Culp)* has used the foregoing plan for routine examination of the legs and for heparin therapy in the management of all patients on one urologic service at the Mayo Clinic. So far, the results have been just as gratifying as they were at the Henry Ford Hospital.

From August 7, 1950, to April 1, 1951, 220 separate operations were performed on 209 patients on this service. This wide variety of surgical procedures involved all segments of the genito-urinary tract (table 7).

Fatal pulmonary embolism has been avoided even though phlebothrombosis developed in 3 patients after segmental resection of the bladder, perineal biopsy of the prostate, and nephrectomy, respectively. Each recovered after ten days of treatment with heparin and no one had any bleeding or embolic complications. A fourth patient had a small pulmonary infarct after suprapubic diverticulectomy but continued to have negative findings relative to the legs. The embolus may have originated in the pelvis. There were no further embolic manifestations after anticoagulant therapy.

Fuller and Barker[15] have found that vitamin K_1 is much more effective than earlier preparations in counteracting the anticoagulant effect of dicumarol. The less expensive dicumarol may replace heparin after the first few days in the therapeutic plan now that it has an effective antidote.

Burke and Wright[16] insist that neither heparin nor dicumarol is an ideal anticoagulant and advise further clinical trials with tromexan, a Swiss drug that is now available in this country. They report that this new oral preparation "appears to have the advantages of more rapid utilization and more rapid cessation of action than dicumarol, although the mode of action is similar in that it produces a hypoprothrombinemia."

The constant search for better anticoagulants is most commendable and future discoveries may dictate significant changes in prophylaxis against pulmonary embolism but no plan of treatment will be effective unless phlebothrombosis is recognized early enough to be treated promptly.

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* A consultant in urology, Mayo Clinic, Rochester, Minn. since August 1, 1950.

[15] Fuller, B. F. and Barker, N. W.: Minnesota Med. **34:** 326–328, 1951.

[16] Burke, G. E. and Wright, I. S.: Circulation. **3:** 164–170, 1951.

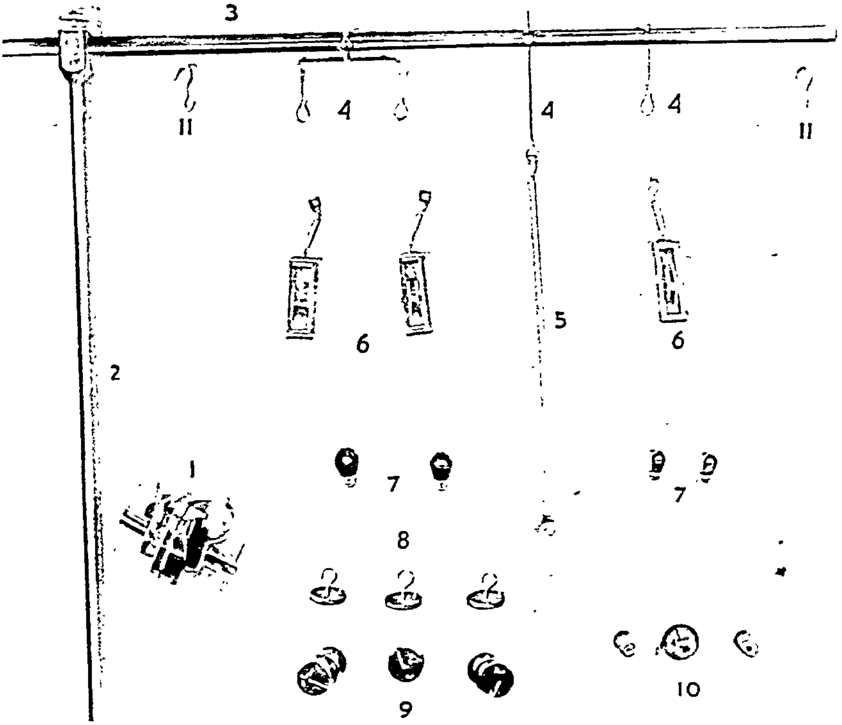

FIG. 1. Component parts of balanced suspension apparatus. Identification of parts by number is listed in text.

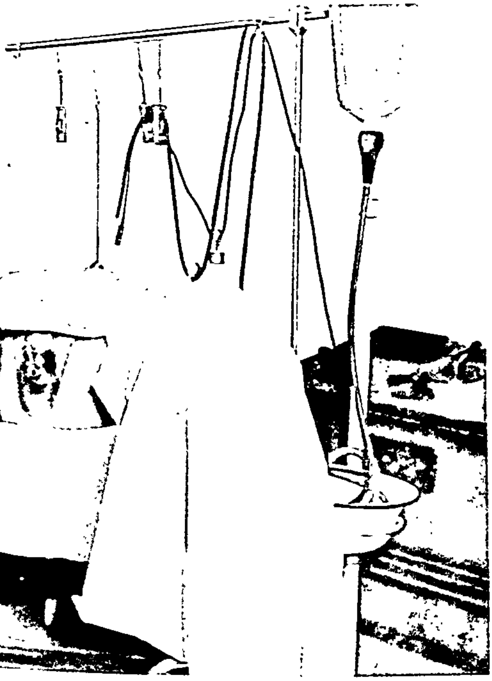

FIG. 2. Suspension Instrument moved to one side to prevent interference with moving [illegible] table.

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BALANCED SUSPENSION FOR FACILITATION OF ENDOSCOPIC INSTRUMENTATION

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The prevention of tautness or friction drag and undue redundancy of any of the supply lines connected to the resectoscope as well as maintenance of this instrument in position seems a worthy objective.

For these purposes the author has designed an apparatus which consists of the following parts (fig. 1):

1) One table clamp for adjustment and retention of the vertical rod.

2) One straight or L-shaped vertical rod with fenestra and screw clamp at its upper end for adjustment and retention of the horizontal rod.

3) One horizontal rod perforated in three places for stem hanger placement.

4) Three stem hangers with loops for connection with pulleys and instrument leash. Two stems are fitted for rotary movement, whereas one stem, attached to a cross-piece for connection with two pulleys, is provided with a set screw for stationary and directional adjustment.

5) One spring leash provided with slide-on clamp to fit onto the endoscopic instrument for the purpose of holding same in situ.

6) Three rod pulleys. These are suspended by coil spring from the stem hangers.

7) Four counter-weight (upside-down) pulleys. Their frames are cut for application to lines and weight-holders. Two sizes of water-line pulleys to fit diameter of rubber tubing usually used for this purpose.

8) Three weight holders.

9) Two sizes of coin-shaped weights perforated and slotted for secure application to the weight holder.

10) Three half-split rubber corks of sufficient size for impingement against pulley frames. One cork, applied to each line between resectoscope and rod-pulley, functions as a stop for lines when these are disconnected.

11) Two solid spring-like retention clips. These are applied around the horizontal bar-ends for line suspension at a fixed point.

Counterbalance is effected by retention of all lines before the latter are passed through the rod suspended pulleys in such manner as to produce U-shaped line loops. To the most dependent area of U-line formation the counterweight pulley is applied.

For sturdy and lightweight construction, the rods are made of stainless steel-tubing. This type steel was also used in making all coiled springs, stem-hangers and rod pulleys for rustproof purpose.

Rod pulleys are of special design in that their wheels are mounted by pivots rather than by ball-bearings, so that oiling of these parts is not required and

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The material on which this paper was based was exhibited at meeting of American Urological Association at Chicago, Ill. May 20, 1951; also read and exhibited at meeting of North Central Section, American Urological Association, Toledo, Ohio, October 4, 1951.

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WHAT OF THE FUTURE?

ELMER HESS

Many of the great surgeons of the past climbed to medical fame as a result of their work on the urinary tract. I call your attention to Bigelow, Gross, White, Martin and some others in this country, as well as their contemporaries in Europe. This was also true in the Ancient World. In the Hippocratic Oath the ancient physician swore not to do operations upon the urinary tract but to leave this surgery to be done by those especially skilled in the maneuver.

The founders of American urology were interested, for the most part, in the diagnosis and treatment of venereal disease. As the specialty of urology developed and the American Urological Association grew, men interested in venereal disease and general surgeons interested in the surgery of the urogenital tract naturally came together to exchange their points of view. As a result of this interchange of scientific knowledge, the modern urologist developed into a medico-surgical unit for the diagnostic, medical and surgical treatment of urological problems in both sexes. The development of Edison's cold incandescent lamp made the cystoscope of practical value as a diagnostic and operative instrument. As a medical student I can remember when Dr. Nicholson, Assistant Professor of Obstetrics at the University of Pennsylvania, used to do about two cystoscopies annually and every one turned out to watch the operation. Wagers would be made by the students as to whether the then hot lamp of the cystoscope would not burn a hole in the patient's bladder, necessitating an emergency cystostomy. Many of the older men in those days did not develop into urological surgeons but depended on the general surgeons for their operative work. Later many of these men devoted all of their time to the urinary tract and thus was born modern urology.

In the first issue of the *Journal of Urology*, June 1917, there is a voluminous paper on the operative treatment of urethro-rectal fistula. The authors? Whom do you suppose: the eminent Hugh Young and Harvey Stone, budding general surgeon.

In June 1921, shortly after the first pyelograms were made possible by the use of the silver and iodide salts, William F. Braasch, in his presidential address before this society, stated: "Whether the urologist should also take care of the surgical treatment in his field is a question for argument, and I believe not of fundamental importance. I am frank to confess, however, that I believe there are many reasons in favor of the urologist taking care of his own surgery."

In the discussion, Dr. A. L. Chute of Boston, said: "The general surgeons feel, with a few exceptions, that they can do the operation on urinary cases better than we can and the after-care equally as well."

John Caulk said: "I suddenly broke into applause when Dr. Braasch spoke about the urologist doing his own surgery."

Herman Kretschmer said: "I am very glad to hear Dr. Braasch say that he is of the opinion that the urologist should do his own surgery."

Presidential address read at annual meeting, American Urological Association, Atlantic City, N. J., June 25, 1952.

their sensitivity remains unaffected by immersion in water. The pulley wheels are grooved to sufficient depth for line retention.

The horizontal rod and all material connected therefrom may be sterilized in antiseptic solution, steam or boiling water. For sterilizers not long enough to receive the horizontal rod, the latter can be made up into two joinable sections.

Since there are no delicate parts, repairs or replacements should be absent or minimal.

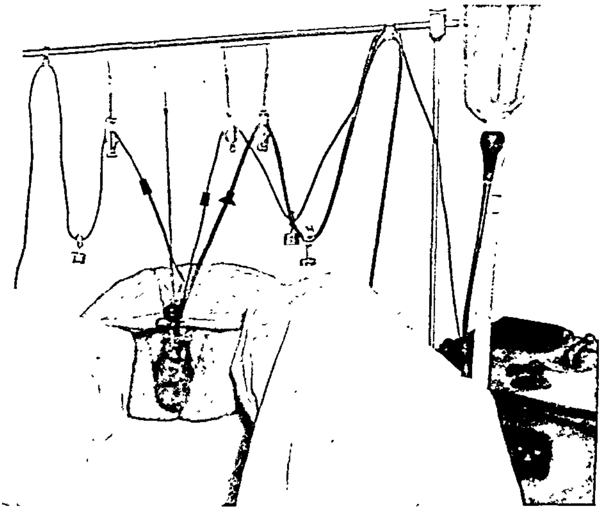

FIG. 3. Suspension apparatus connected to endoscopic instrument in situ

The apparatus, built and arranged as described, readily lends itself to the following multi-adjustments:

1) Adaptability to all tables (on right or left side) and line diameters.

2) Movability of rods in all directions for proper position of the apparatus as well as its noninterference with moving patient on or off table (fig. 2).

3) Obtainment of correct degrees of counterbalance which may vary with each line.

4) Easy and rapid assemblage and disassemblage of all parts. This work may be delegated to one of the supervisory nurses.

SUMMARY

Essential and practical requirements have been met in the design and satisfactory use of the mechanism herein described. By this means there is maintenance of proper direction and counterbalance of all supply lines to the endoscopic instrument as well as elimination of undue friction against drapes or other equipment by these lines (fig. 3).

Though balanced suspension is an accessory apparatus, the technical advantages gained by its use in attainment of greater ease and flexibility in such instrumentation as the performance of transurethral resection, has been found to outweigh the small amount of time required in setting up this equipment.

1422 Euclid Ave., Cleveland 15, O.

the men in the training programs. Here too might be the central office of the American Board of Urology and thus save that group considerable overhead.

At the present time our Secretary's office is costing us approximately $16,000 a year and it is my conviction that it would cost very little more than this to maintain a central home office and that each of the Sections would be willing to finance a certain proportion of this expense.

The financing of a central office can be done in one of two ways: 1) by a membership assessment, or 2) by forming a financial committee in each Section to raise the money by voluntary subscriptions. This would give us sufficient funds to buy property and equip it for our needs.

If a central office is thus acquired, properly staffed, and financed to do the work suggested, it would be a place where the Executive Committee could meet oftener than once a year, and if the work of this committee continues to increase as it has in the past this will be a necessity. The problems that come before the Executive Committee at the annual meeting, although given all the attention that the time allows, are often very hastily considered and the best answers may not always be available. To study more thoroughly and discuss more carefully the pertinent problems brought before the Association, I would suggest that one of two policies be followed:

1. A committee of not less than two and not more than five men elected by each Section should meet prior to the annual meeting. The duties of this Committee would be to study and discuss various organizational problems handed to them by individuals, the various Sections and/or the Executive Committee. After full discussion these problems would then be referred to the Executive Committee with recommendations for official action, or

2. The creation of a House of Delegates of not less than three and not more than seven members from each Section to whom all the affairs of the Association would be referred for study, deliberation, and recommendation. A directive from this House of Delegates would authorize the Executive Committee to carry out the wishes of the House of Delegates during the interim between the annual sessions. The House of Delegates would give the Executive Committee authority to act in the interim in the event of an emergency. The creation of such a House of Delegates would require a very few basic changes in the organization of the Sections. Since no one should vote in a Section on actions to be taken by the parent organization unless he is a member of the American Urological Association, sectional active membership would have to be changed by the Sections to include only those who have attained full membership in the parent body. The status of all other Section members would be that of non-voting Associates.

I realize that this is going to require an enormous amount of work but one or the other of these suggestions is a "must." If it is decided that reorganization according to either one of these methods is advisable, then it would also be proper to have this committee or the House of Delegates meet Friday and Saturday before the annual session, together with the Executive Committee to decide how the affairs of the Association shall be conducted during the ensuing year. This sort of program would be impossible unless the Sections all agreed that this was

Dr. A. J. Crowell said: "Our work is subdivided. I do the surgery—Dr. Thompson does the diagnosis with Dr. McKay."

At least these men, most of whom you all have known, many of whom are still living, fought the good fight to bring to the urologist not only the privilege of doing diagnostic work but the surgery and postoperative follow-up as well. Today few general surgeons encroach on the urological field. What a debt of gratitude we of today owe to these pioneers for the creation of this great urological specialty.

When I first limited myself to the practice of urology in 1921, the general surgeons would inform prospective patients that to be seen in my waiting room labeled them as having gonorrhea and of low morality. Those were trying days for this young specialty. While the gonococcus was considered by the urologist as just another member of the family of pus-producing organisms, it remained our cross until the advent and use of the antibiotics during the last decade. When the cure of this disease was made easy by the discovery of chemotherapeutic agents, the internists and the general practitioners took over and left for us only the sequelae of the infection which require surgical skill. We had already gladly consigned syphilis to the dermatologist, the internist, and the neuro-psychiatrist. From this lowly past we have evolved into one of the outstanding diagnostic and surgical specialties and in the short span of fifty years. For much of this we can thank our pioneering confreres and our outstanding scientific journal. Today our younger men are so equipped that they have no superiors in the surgical and scientific world and with the acquisition of this adult growth the specialty is now of age.

Remembering the address of Thomas D. Moore last year, one must realize the enormous growth of the American Urological Association and its scientific importance in the field of the medical specialties.

Now, what about the future? Here are the possibilities.

There were many replies and suggestions to the News Letter which I sent out in December 1951. As a result of the answers to my questionnaire it is time that this Association took stock. First, you have requested that a central home office with a full-time executive secretary and staff be established. This is more important now than ever before because you have created the Urological Research Corporation, under the laws of the State of Ohio. The directors, I hope, will be selected from nominees from each Section of our national association. The Corporation to be effective will have to have an executive secretary and a central office. It is feasible that the offices of both the American Urological Association and the Corporation be one and the same. It stands to reason that a central office could take a great deal of the work off the already over-burdened shoulders of the secretaries of the various Sections and that much of the business of the various Sections could be transacted from such an office. This central office would also furnish meeting places for the various committees. Here too would be the repository for our archives. The records of the various accredited institutions where approved residencies are available would be filed here and our officers could work with these various institutions and help in the proper distribution of tion and in the Sections should not be based upon Board certification. This should merely be an asset in the qualification of an individual for membership.

There is a great deal of misinformation concerning our splendid journal. I have a great many letters making suggestions about the *Journal of Urology*. Some men want news added; others want the Journal to have an editorial policy; others want the business transactions printed in the Journal so that every one may be informed as to where and how their money is being used; just what are the duties of the various committees and what their reports have been; and what in general are the policies of the Association. Others desire summaries of the papers in Spanish for the benefit of our Spanish-American friends. All are entitled to have answers to their these questions.

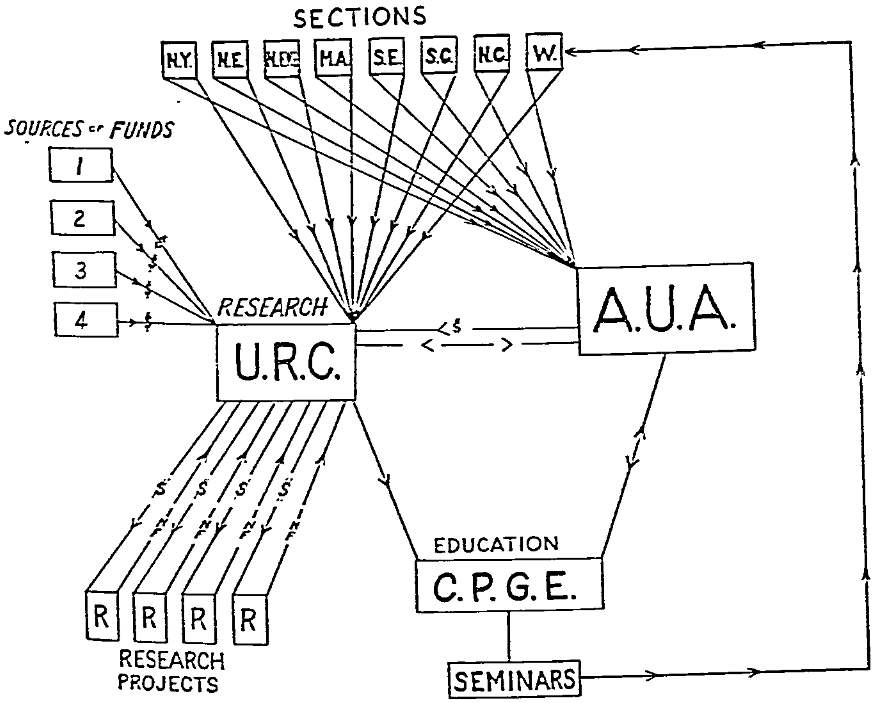

FIG. 1.

What most of our members do not know is that if the *Journal of Urology* did these things the pages would be doubled and to fulfill all of these requests would vastly increase the expenditures of the Association. Few of us realize how well the late Hugh Young planned, and I can inform you that the contract which he made for the publication of the official Journal of the American Urological Association under no circumstances should be disturbed. Under the leadership of the Editor, Cap Colston, and the Associate Editor, Hugh Jewett, the *Journal of Urology* has been greatly enlarged within the limits of our contract without jeopardizing our financial arrangements with our excellent and cooperative publishers, the Williams and Wilkins Co.

the proper way to handle the problem. In my opinion, this is the only way to keep the membership of the organization completely informed as to national policies and to permit the membership to know what is being done and why, and to have each member feel that he is participating in the actions of the parent body.

Believing as I do that most of our problems must be solved at the local level and that the Sections should each be permitted to be their own law-makers, the solving of the above problems of necessity would require a similar voluntary reorganization on the part of each Section.

As you all know, medical education in general, and urological education in particular, has been one of my hobbies. We have at the present time, under the chairmanship of William Braasch, a committee for postgraduate study. We have held many postgraduate seminars throughout the country during the past few years, under the management of the various Sections, with some financial help from the parent organization. All of these seminars have been very well attended and many have been financially profitable. After our experiments with these postgraduate seminars, I am firmly convinced that the entire program should be organized under the supervision of our postgraduate committee. There should be not less than one nor more than two seminars annually. The local group should not be responsible for anything but the hotel accommodations, the equipment and the meeting place. The faculty and program should be the responsibility of the national post-graduate committee. I feel sure that if we have a central home office with an executive secretary that these seminars would be self-supporting and might be the source of some revenue to help run the home office.

The urological research foundation has had to be set up separately from our Association because of the tax problem. I might suggest that our own constitution be changed so that the American Urological Association can receive tax-exempt funds. The foundation will receive monies from various sources. It seems illogical for us to ask our friends to make large contributions to this foundation unless we are willing to make some contribution ourselves; therefore, I suggest that we take from our capital funds the sum of $25,000 as our organization's contribution to the foundation. I also suggest that ways and means be provided for voluntary contributions from our members who may be equally interested in this educational work. Then, as I understand it, the information which the urological foundation obtains from the various research problems should be funnelled back to the organization membership through the committee on postgraduate study. The slide (fig. 1) I now show will graphically express my conception of the American Urological Association's relationship to both the research foundation and the committee on postgraduate education.

All in all, the American Board of Urology has done a most satisfactory job. There have been a great many suggestions and some criticisms of its actions, but at the present time I have nothing to offer except to say that the parent organization has a definite responsibility toward the Board of Urology. Suggestions which the Association believes will improve our relationships with the Board should be forthcoming. It is my confirmed opinion that membership in the parent organizaforgotten that there are other requisites that are mandatory besides pure science. We must be doctors first.

Scientific accomplishments alone do not make us decent members of civilized society. We found out in these last few momentous years that pure science was materialistic and that without spiritual values was worthless. We seemed to have forgotten that we must give to the sick individual who consulted us for relief, something very intangible but something very important, i.e., confidence. The dictionary describes confidence as "full trust", et cetera. I like those two words "full trust". Your patient cannot, under any circumstances, have full trust unless there is a definite spiritual bond between you. This relationship makes your scientific efforts wholly successful and satisfactory. This has nothing to do with money. The great reward is the personal satisfaction engendered by you, the physician, in the heart, mind and soul of the sufferer. This is completely absent when commercial values are more important than service or when a heartless, soulless corporation is furnishing medical care to the ill public, and I care not whether that corporate body is a government agency or a commercial clinic. There is, of course, and in a practical world we must admit that there should be, a definite place for governmental medical services and for insurance programs to help those who suffer meet some of their financial obligations, but the service to the individual sufferer must always be a personal sanctified one in which confidence and science are blended toward the perfect physician-patient relationship. To deny this is to deny all that real religion has taught men since the beginning of time. As a man is in his heart, so is he.

We do not live alone. We must adjust ourselves to our problems. We must face them with courage, enthusiasm and imagination. We have established ourselves upon a firm scientific foundation. We must continue to develop all of our educational efforts for ourselves and those who will follow us in the future. We must support with all our resources the new urological research foundation and we must not be afraid to spend money on post-graduate education. Each of us has been especially blessed in that we are important members of the great medical profession. We should continue to support as we have in the past the work of the American Medical Association, many of whose leaders have been prominent members of the American Urological Association, and all other medical and surgical groups whose object it is to maintain high standards of practice, education and hospital-physician relationships. We have attained greatness because we have been free to develop our specialty. We have overcome many hazards and obstacles during the past fifty years and we wish to continue to develop in the future under the free enterprise system. Is all this enough? I say NO. We must not only be good doctors but good citizens. This type of scientific development would be impossible under the bureaucratic Federal control of medicine.

As Chairman of the Council on Medical Service and the Committee on the Extension of Hospitals and Other Facilities of the American Medical Association, I know the thinking of the parent body.

Some of our specialty societies, not particularly interested in economics,

Here are the facts:

1. In order that the Journal of Urology remain self-supporting and pay operating expenses, it is necessary by the terms of the contract with the publishers to limit the number of pages published per year. If the number of pages is limited to 1700, the *Journal of Urology* not only can pay its expenses, but add a small profit to the *Journal's* reserve fund. If the members of the Association believe that more articles dealing with urological subjects should be published by the *Journal* each year, it is a matter of simple arithmetic to see that each article published would have to be cut to the bone.

2. Dissatisfaction has been expressed in certain quarters concerning the delay in publication of some articles. There are three fundamental reasons for this delay which are not understood clearly by the urological profession. These are:

a) Papers presented at the meetings of the various Sections are scrutinized individually by the members of the local editorial committee. This requires a long period of time, and in some instances necessitates forwarding papers back and forth from city to city among different members of the local editorial committee. As a result of this, in some instances months elapse before the papers presented at the Section meetings are received in the editorial office.

At the meeting of the Mid-Atlantic Section, Hugh Jewett suggested that the editorial committee meet at the conclusion of the scientific session and immediately recommend to the secretary those papers considered suitable for publication in the *Journal*. If this practice were followed in the other Sections, this fundamental cause of delay would be eliminated.

b) Sections which publish Transactions add a considerable burden to the work of the editorial office. Many of the papers are not acceptable for publication in the Journal. Each paper has to be carefully edited, put into readable English, and sometimes even returned to the author for many corrections. Lengthy discussions have to be similarly edited. The extra work involved in these matters is responsible for some of the delay.

c) Many articles accepted for publication in the *Journal of Urology* each year arrive at the editorial office in a form unsuitable for immediate publication.

If we had a central office it might be possible to edit separately the Transactions of each Section and to send out a report of the business sessions of the society as separate publications.

There have been many other suggestions in your correspondence which have distinct merit. These will be compiled and turned over to the proper committees for their study and consideration.

Today the American Urological Association is the largest and greatest organization of scientific urologists in the world. We have fought and won our scientific freedom from the general surgeons. The fight has been long and at times bitter, but we have survived and succeeded because we have been able to convince the profession and the public that superior results have demonstrated our right to leadership in the diagnosis and treatment of urological diseases. We, like all other members of the great specialty societies and of the American Medical Association, had become so smug in our scientific accomplishments that many of us had neglected job to do if they were to save their profession from regimentation and degradation. Finally, stung into action, the sleeping giant (the medical profession) awoke and without realizing its power became non-partisan in the development of its political strength. The physicians, their wives, their friends in the allied professions and in those industries directly connected with medicine, and others, joined hands and went to work. The result was the defeat in 1950 of all but one or two of the candidates of both parties in almost every State in the Union who stood for the Socialist programs of the present Washington administration. In many Democratic areas, non-administration Democrats overwhelmingly defeated administration Democrats. In other areas Republican opponents of National Socialism defeated tried and true New Deal or Fair Deal Democratic incumbents who preached and voted for these socialistic measures. In all these campaigns the awakened physician took a leading part. At last the doctor asserted himself as a citizen. No longer will he be apathetic and indifferent to the political life of our country of which he of needs must be a vital part. The threat of Socialism is still with us and the proponents of socialized medicine are forever at work. Our every action will be watched in the future. The enemy will constantly search for a weakness here and there in our defenses. Don't fool yourselves that the struggle is over because it has really just begun. The politician may buy votes by promising the favors of a so-called Welfare State, but if you and I constantly demonstrate at the bedside and in the office that we have the public interests at heart, there will never be enough people to make a Welfare State a possibility.

For your information during the past few years two powerful labor leaders have publicly renounced the Federal control of medicine—so-called Socialized Medicine. They are Dave Beck of the Teamster's Union and Hutchinson of the Carpenter's Union.

As a profession we have many friends in labor. As a matter of fact a great deal of our work is done for those who believe in and belong to the unions. Many of their members are as opposed to the Federal control of medicine and Socialism as we are. It is the distinct responsibility of those of us in urology to so serve this great mass of people that the rank and file of labor will become convinced that only through the efforts of a free medical profession may high quality medical service be rendered to their people.

The American people have enjoyed the best quality medical care that has ever been rendered to any people at any time in the history of the world. It is our job to take care of those who suffer and to see that no one shall be denied good medical services because of any financial barrier between us and those who suffer.

We are in politics to stay and this is a year when every one of us must cooperate to the fullest in our political endeavors. We have at last realized that as individuals we must be good citizens. We must not only register and vote, we must get others to do the same. We must work day and night to influence our friends and patients to vote against those who would change our form of government. We must work and vote for those candidates for public office who are pledged to preserve the constitutional rights of our people. By being scientists, recognizing spiritual values, and doing our individual duties as citizens, we can have criticized the actions of the American Medical Association. Since the parent body is the only one that truly represents all medicine, we should be active in and support the measures taken for our protection.

Blindly, we have gone our way developing our science, not always understanding too keenly our spiritual needs, too often completely satisfied in a smug sort of way with ourselves—more or less content with our individual lives and accomplishments—often self-centered and conceited—always in the past the recipients of special favors from the authorities—respected and idolized by our patients, for the most part—assured, because we were doctors—of social position and a certain financial stability—jealous of our position and completely oblivious of everything around us but our scientific job. Then came the explosion and medicine tottered on its two legs—science and spiritual values—and in the twinkling of an eye we almost became the slaves of governmental bureaucracy. Socialism, Communism, call them by whatever name you will—they are synonymous. Realizing that only by the subjugation of the medical profession could their selfish aims be realized, the advocates of socialistic philosophies attacked American medicine from the front, both flanks and the rear. American medicine almost fell. Only the vision and fighting ability of a few leaders in those desperate days staved off the disaster. Conservative, self-satisfied, apathetic physicians shrugged their shoulders. Some went over to the enemy. Others didn't believe the rumors. They had heard them often before, but nothing had ever really happened to disturb their complacency, but now the "do-gooders," some welfare workers, some religious groups, and many other good honest people, including many laborites, fell for the subtle propaganda of the Socialists and the social reformers—yes, even that of the Communists, namely, that the profession was interested only in money and not in the sick, else they would not buck every single thing that they (the welfare people) were trying to do for the poor and downtrodden in the human family. The public also fell for the slogan, "Something for Nothing".

We, as a profession, were so completely self-satisfied with ourselves and so busy that few of us realized that this thing called Socialism which was threatening us, was partly our own fault. Our medical leaders had great difficulty in arousing the profession as a whole, and it did seem that when we finally pitched into the battle it was already lost. Our biggest job was not to educate the public but to educate the doctor. The educational campaign of the American Medical Association was launched to educate the public. This seemed hopeless, but gradually the Ph.D.'s and others in the Social Security Administration of the Federal government, carrying a relentless propaganda campaign against the organized medical profession, financed with your tax money and mine, succeeded in doing just one thing. They overstated the heartlessness of the physicians. The public, believing in their own doctors, soon realized that their physicians were just the opposite of the propagandized picture and began to question the sincerity of the attacks. The physicians, smarting under the unfair misrepresentation of the propagandists, began to realize their smug complacency in matters pertaining to government and gradually, oh, so gradually, they awoke to the fact that it wasn't enough to be scientific and spiritual, but they had a long

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ENDOCRINE FACTORS IN CANCER

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This lecture is dedicated to the memory of Ramon Guiteras, one of the founders of the American Urological Association; may he always be remembered with pride and affection by our members. May he rest in honor and in peace.

Recent years have seen great progress in the understanding of cancer and hence of its control. Certainly advances of some magnitude have been made in unravelling the endocrine aspects of tumors. Hormones are significantly involved in the causation, the prevention and the treatment of a great variety of cancers. These are the topics of the present paper.

ENDOCRINE CAUSES OF CANCER

The basis of endocrinology is that certain glandular structures synthesize chemical substances which excite activity in target cells at some distance. Dependence is the key concept of activity in endocrine targets. The target cells of hormones are of two types, those that are end organs and those which themselves are synthetic factories of other hormones.

Among the dependent synthetic stations are the gonads, the adrenal cortex and the thyroid, and all of these are largely under the control of the anterior pituitary. The great characteristics of these intermediary synthetic cells is that the hormones which they elaborate constitute a feedback mechanism (to use the language of communication experts) which inhibits the hypophyseal or other prime mover. This is analogy: except among specialists the mind gladly shuns abstract thought even at the cost of physical work. We find it much more congenial and less wearing to visualize complex states in terms of familiar and homely examples and these are quite acceptable so long as the limitations in precision are appreciated. Feedback circuits are now extensively utilized by engineers and the feedback concept is useful in visualizing endocrine physiologic control devices of the body. To cite a simple and unsophisticated electrical case of feedback (fig. 1) in "keeping the house at seventy" a closed cycle feedback device working through the thermostat prevents the furnace from burning down the house. "The closing of the feedback loop so that the room temperature controls the furnace drafts which in turn affect the room temperature—the closing of this loop is what causes this type of control to be called 'closed cycle'."[1] The steroid hormones of the gonads, themselves, as a feedback inhibit the overproduction of gonadotrophin by the anterior pituitary[2]; in this case it is apparent that the pituitary itself is a target organ. The inter-relationships are primarily

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The Ramon Guiteras lecture given at the annual meeting, American Urological Association, Atlantic City, N. J., June 25, 1952.

[1] Weaver, W. in MacColl, L. A.: Fundamental Theory of Servomechanisms. New York: D. Van Nostrand Co., 1945.

[2] Moore, C. R. and Price, D.: Gonad hormone functions and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex-hormone antagonism. Am. J. Anat., 50: 13–71, 1932.

build the future on a solid foundation. The American Urological Association as an organization must not and should not become entangled in partisan politics. We must take our stand along with the American Medical Association in opposition to any legislation advocating Socialism at the Federal level. Likewise we as individuals must oppose those of any political party who support the principles of National Socialism. The die is cast.

A REQUEST FOR THE APPOINTMENT OF OTHER COMMITTEES

All of these reorganization problems and the suggestions for the future cannot be solved over night and for this reason I sincerely hope that at the business meeting some one will move that President-elect Cahill be empowered to appoint a committee of not less than two and not more than four men from each Section to meet at the earliest possible date for as long as is necessary, at the expense of the American Urological Association, to study all of these problems herein outlined and after full discussion and study of the voluminous correspondence which I have had from you, to be ready to present a program based on these ideas at the next annual meeting. If the President does not wish to make the appointments personally, the Association might authorize that this committee be formed by electing not less than two and not more than four men from each Section so that they would have the privilege of selecting their own representatives to study these proposals and attempt to find the working answers.

It has been a great privilege to work with you and now more than ever before this Association belongs to you, its members. I commend to you your new President, my friend of many years standing, George Cahill. May Divine Providence guide him so that this Association both individually and collectively may serve the people of this great country with spiritual humility as scientific urologists and our country as good citizens.

8 E. 12th St., Erie, Pa.

in 3 male mice by the injection of an estrogenic hormone. This definitive work has been confirmed many times.* *Estrogen* is the only hormone known to induce breast cancer. By definition any substance which produces squamous epithelium in the vagina of castrate rodents or in the posterior lobe of the mammalian prostate is estrogenic.

In 1937 W. U. Gardner,[4] another giant in the field of cancer experimentation, and also Lacassagne[5] independently observed a high incidence of *lymphoid tumors* in mice treated with *estrogen*. The Gardner tumor has been used profitably by many experimentalists since its discovery.

Cramer and Horning[6] were the first to observe that the administration of *estrogen* for long periods of time, induces chromophobe tumors of the *anterior pituitary*. Such tumors also have been produced experimentally in the pituitary of other animals.

W. O. Nelson[7] and Lipschütz and his pupils[8] discovered independently that *estrogen* produced fibromyoma of the *uterus* and of the peritoneum of guinea pigs. Malignant tumors of the uterine cervix[9] may be induced with *estrogen*.

Matthews, Kirkman and Bacon[10] found that nearly every male golden hamster (but none of the females) treated with *estrogen* developed benign or malignant tumors of the cortex of the *kidney*.

Bonser and Robson[11] discovered that *estrogen* produced benign and malignant interstitial cell tumors of the *testis* of certain mouse stocks.

Moon, Simpson, Li and Evans[12, 13, 14] injected the growth hormone of anterior pituitary in rats for 1⅓ years and observed a considerable number of lymphosarcomas, adrenal cortical neoplasms and ovarian tumors in the recipients. In a closed cycle. Failure of feedback mechanisms to operate is one of the causes of hormonally induced cancer.

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* In order to keep the bibliography within manageable proportions only the discoverers of great effects are cited in this paper. Any mistakes in this regard are attributable to defective scholarship on the part of the author rather than to bad intent.

[4] Gardner, W. U.: Influence of estrogenic hormones on abnormal growths. Occas. Publ. Am. Assn. Adv. Sci., 4: 67–75. Lancaster, Pa.: Science Press, 1937.

[5] Lacassagne, A.: Sarcomes lymphoides apparus chez des souris longuement traitées par des hormones oestrogènes. Compt. rend. Soc. biol., 126: 193–195, 1937.

[6] Cramer, W. and Horning, E. S.: Experimental production by oestrin of pituitary tumours with hypopituitarism and of mammary cancer. Lancet, 1: 247–249, 1936.

[7] Nelson, W. O.: Atypical uterine growths produced by prolonged administration of estrogenic hormones. Endocrinology, 24: 50–62, 1939.

[8] Lipschütz, A., Vargas, Jr., L. and Ruz, O.: Antitumorigenic action of testosterone. Lancet, 2: 867–869, 1939.

[9] Gardner, W. U.: Hormones and experimental carcinogenesis. Acta Union Internat. contre cancer, 6: 124–133, 1948.

[10] Matthews, V. S., Kirkman, H. and Bacon, R. L.: Kidney damage in the golden hamster following chronic administration of diethylstilbestrol and sesame oil. Proc. Soc. Exper. Biol. & Med., 66: 195–196, 1947.

Kirkman, H. and Bacon, R. L.: Malignant renal tumors in male hamsters (*Cricetus auratus*) treated with estrogen. Cancer Research, 10: 122–123, 1950.

[11] Bonser, G. M. and Robson, J. M.: The effects of prolonged oestrogen administration upon male mice of various strains: Development of testicular tumours in the Strong A strain. J. Path. Bact., 51: 9–22, 1940.

[12] Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M.: Neoplasms in rats treated with pituitary growth hormone. I. Pulmonary and lymphatic tissues. Cancer Research, 10: 297–308, 1950.

[13] Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M.: Neoplasms in rats treated with pituitary growth hormones. II. Adrenal glands. Cancer Research, 10: 364–370, 1950.

[14] Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M.: Neoplasms in rats treated with pituitary growth hormones. III. Reproductive organs. Cancer Research, 10: 549–556, 1950.

Examples of end-organ targets of hormonal activity are the breast, the prostate and indeed all of the secondary sex characters. In contrast to the targets which synthesize hormones, the end organs respond to hormonal stimulation in one direction only being unable to modify or relieve the hormonal pressure upon them even when it becomes burdensome or quite intolerable.

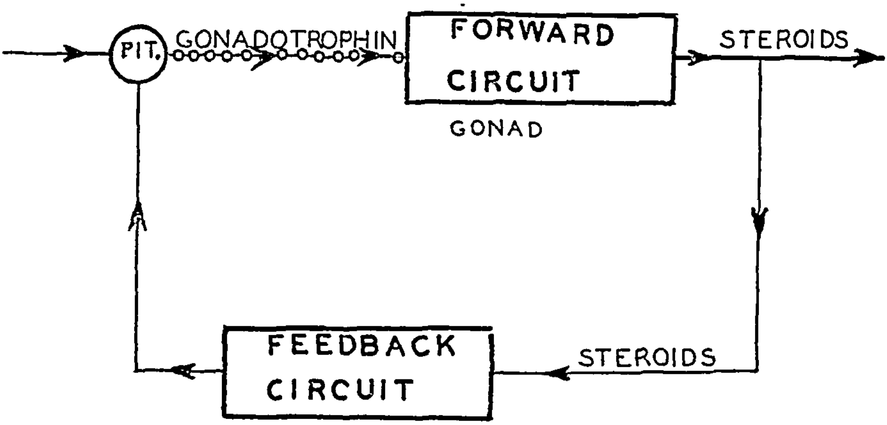

FIG. 1. Analogy of pituitary-gonadal relationship to a closed-cycle feedback electrical circuit.[1]

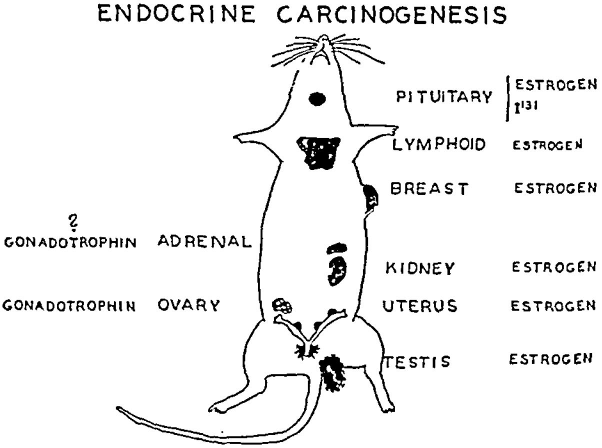

FIG. 2. Schematic representation of endocrine carcinogenesis; site of neoplasm and reponsible hormonal agent are indicated.

Cancer is an abnormal growth process. Hormones cause growth, usually secretion and sometimes differentiation in their targets. Is cancer evoked by excessive stimulation of hormonal growth promoters of all sorts? Is there any specificity for hormones in their capacity to induce neoplastic growth? Let us examine some cases (fig. 2).

A. *Direct stimulation of hormonal end-targets.* In one of the classical experiments in cancer research Antoine Lacassagne[3] produced *mammary carcinoma* discovered for producing pituitary tumors was the chronic administration of estrogen; it is of interest that in the I^{131} treated mice there is an hypertrophy of the ovaries[22] which have the appearance of those of pregnancy and there is a conspicuous stimulation of the uteri of these mice. The possibility exists that *estrogen* is of importance as a primary etiologic agent causing pituitary tumors in this case.

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[3] Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine. Compt. rend., 195: 630-632, 1932.

THE PREVENTION OF CANCERS BY ENDOCRINE MEANS

Many of the neoplasms inducible by hormonal methods may be prevented by appropriate treatment of the host through endocrine modifications. The prophylactic method consists of a relief of hormonal pressure on its target. There are 2 ways to accomplish this: *a*, by restoration of a deficient feedback to the anterior pituitary; *b*, through hormonal competitive inhibition.

a, Restoration of the feedback. Wooley and Little[23] who (with Fekete) so brilliantly produced *adrenal tumors* in susceptible strains of mice through early gonadectomy[24] found that they could be prevented by the administration of *estrogen*.

Gardner[20] discovered that the *ovarian tumors* which occur following total body irradiation in mice may be prevented by the administration of *estrogen*; testosterone was ineffective.

The development of gonadal tumors in an intrasplenic transplant is prevented by retention of the contralateral gonad. In this situation the splenic gonad remains atrophic although it can become stimulated during pregnancy.[17] The function of a normal gonad through its hormone production prevents contralateral cancer in a damaged gonad.

b, Competitive inhibition of steroidal hormones. The neoplasms which are induced by estrogen may be prevented by testosterone.

Nathanson and Andervont[25] using female C_3H mice which had been bred once found that *testosterone* reduced the incidence of mammary cancer from 100 per cent in the controls to 29 per cent. Androgen had no effect on established mammary tumors of mice.

Gardner, Doughtery and Williams[26] found that 11.9 per cent of mice injected with various estrogens developed leukemia; the administration of *testosterone* in addition to estrogen reduced the incidence of lymphoid tumor to 2.3 per cent, approximately the value obtained in uninjected mice.

Lipschütz et al.[8] could prevent estrogen-induced uterine and peritoneal fibroids by the simultaneous injection of *testosterone* or *progesterone* together with the estrogenic agent.

[22] Furth, J. and Burnett, Jr., W. T.: Hormone secreting transplantable neoplasms of the pituitary induced by I^{131}. Proc. Soc. Exp. Biol. & Med., 78: 222–224, 1951.

[23] Wooley, G., Fekete, E. and Little, C. C.: Mammary tumor development in mice ovariectomized at birth. Proc. Nat. Acad. Sci., 25: 277–279, 1939.

[24] Wooley, G. W. and Little, C. C.: Prevention of adrenal cortical carcinoma by diethylstilbestrol. Proc. Nat. Acad. Sc., 32: 239–240, 1946.

[25] Nathanson, I. T. and Andervont, H. B.: Effect of testosterone propionate on development and growth of mammary carcinoma in female mice. Proc. Soc. Exp. Biol. & Med., 40: 421–422, 1939.

[26] Gardner, W. U., Dougherty, T. F. and Williams, W. L.: Lymphoid tumors in mice receiving steroid hormones. Cancer Research, 4: 73–87, 1944.

further series of experiments[15] hypophysectomized rats were treated similarly for about 1 year but there was in this instance almost complete absence of neoplasms despite continuous body growth. These careful observations indicate that the presence of the pituitary gland is essential in the production of neoplasms following administration of growth hormone. They reveal that the pituitary growth hormone *per se* is not an important cause of neoplastic growth.

B. *Cancer due to deficiency of hormonal feedback mechanisms.* The Biskind's[16, 17] observed that transplantation of the ovary to the spleen in rats led to ovarian tumors provided the opposite ovary has been removed. A regular sequence of events occurs after intrasplenic ovarian transplantation in castrate rats. After the initial inflammatory reaction has subsided there is a constant development of new follicles which luteinize; subsequently granulosa cell tumors and luteomas form. In these rats the pituitary is of the castrate type and the uterus is atrophic. The portal circulation leads the ovarian estrogens to the liver where they are inactivated; since the feedback steroid mechanism is destroyed the anterior pituitary misjudges the hormonal status of the organism, interpreting it to be deficient in steroid hormones and so increases its stimulatory function. Consequent excessive *pituitary gonadotrophin* production leads to cancer in the *ovary* which has been reduced to the state of an hormonal end-target.

Furth and coworkers[18, 19] found that roentgen irradiation of mice with 200–400 *r* regularly leads to *ovarian tumors.* When the ovaries are shielded from irradiation ovarian tumors fail to develop. Also, ovarian tumors may be produced by excising the ovaries, irradiating them *in vitro* and replacing them[19] without general body irradiation. It is believed that irradiation causes ovarian damage with a resulting deficiency of the feedback mechanisms which in turn leads to excessive production of *gonadotrophins.* The ovarian remnant bombarded by gonadotrophins undergoes the neoplastic transformation. The tumors may be prevented by the administration of *estrogen*[20] to the animal reconstituting the feedback.

Another method of producing *pituitary tumors* has been discovered recently. Gorbman[21] observed that destruction of the thyroid gland of mice by I^{131} causes chromophobe tumors of the pituitary in high incidence. Apparently the elimination of thyroid hormones as feedback pituitary inhibitors causes neoplastic change in the pituitary. It will be recalled that the first experimental mechanism is self-regulating; likewise these tumors fail to regress under attempts at hormonal therapy. *Anti-androgenic* control through orchiectomy or by treatment with estrogenic compounds inactivates androgen-dependent tumors. Orchiectomy eliminates the greatest androgenic supply of the human male which originates in the testis. Estrogen has a variety of activities, mostly favorable to the host who has prostatic cancer; it decreases the secretion of gonadotrophins by the pituitary; it inhibits androgens competitively; it has a direct action on the cells of certain prostatic cancers. Here estrogen is not carcinogenic but carcinostatic. Estrogen however causes mammary hypertrophy and thereby creates a soil wherein prostatic cancer may metastasize; cancer never metastasizes to the normal male breast but does so not infrequently to the male mammary gland hypertrophied by estrogen treatment. Also, estrogen, at least in the rat, causes adrenal cortical hypertrophy which is not always desirable.

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[15] Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M.: Neoplasms in rats treated with pituitary growth hormone. V. Absence of neoplasms in hypophysectomized rats. Cancer Research, 11: 535–539, 1951.

[16] Biskind, M. S. and Biskind, G. R.: Development of tumors in the rat ovary after transplantation into the spleen. Proc. Soc. Exp. Biol. & Med., 55: 176–179, 1944.

[17] Biskind, G. R., Kordan, B. and Biskind, M. S.: Ovary transplanted to spleen in rats: The effect of unilateral castration, pregnancy, and subsequent castration. Cancer Research, 10: 309–318, 1950.

[18] Furth, J. and Furth, O. B.: Neoplastic diseases produced in mice by general irradiation with x-rays. I. Incidence and types of neoplasms. Am. J. Cancer, 28: 54–65, 1936.
Furth, J. and Boon, M. C.: Induction of ovarian tumors in mice by x-rays. Cancer Research, 7: 241–245, 1947.

[19] Gardner, W. U. Personal communication.

[20] Gardner, W. U.: Ovarian and lymphoid tumors in female mice subsequent to roentgen-ray irradiation and hormone treatment. Proc. Soc. Exp. Biol. & Med., 75: 431–436, 1950.

[21] Gorbman, A.: Functional and structural changes consequent to high dosages of radioactive iodine. J. Clin. Endocrinol., 10: 1177–1191, 1950.

When anti-androgenic treatment, especially orchiectomy, is exhibited in cancer of the prostate the results fall in 3 categories: *a*, no effect on the carcinoma—the neoplasm not being dependent on testicular hormones; *b*, regression of the primary neoplasm and its metastases; *c*, regression of the primary tumor with progression of the metastases. Category *c* will be considered further.

The Adair school[33] has shown that cancer of the *male breast* frequently regresses spectacularly after excision of the *testis*. The lesion does not undergo regression when the patient is treated with estrogen.

Beatson[34] showed that cancer of the *female breast* can undergo regression after excision of the *ovaries*.

Cancer of the female breast has been found to respond favorably both to *androgen* and *estrogenic* hormones. Both methods of treatment are empirical. Ulrich[35] demonstrated some regression of mammary cancer after treatment with testosterone but the proof offered was not rigorous or convincing and this therapeutic method was not adopted extensively until the publication of F. E. Adair and Herrmann.[36] Certain mammary tumors regress when the patient is treated with *testosterone*. Haddow and coworkers[37] found that the soft tissue lesions of mammary cancer often regress after treatment with *estrogen*. The amelioration of the disease with estrogen was somewhat surprising to many since at least in rodents estrogen is a cause of mammary cancer. Also the regression of this lesion after ovariectomy has been thought to be due to elimination of estrogen.

It has been found that certain mammary and prostatic tumors are dependent on *adrenal* function. Nothing could be done about adrenalectomy in man however

[33] Farrow, J. H. and Adair, F. E.: Effect of orchidectomy on skeletal metastases from cancer of the male breast. Science, 95: 654, 1942.

[34] Beatson, G. T.: On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment with illustrative cases. Lancet, 2: 104 and 162, 1896.

[35] Ulrich, P.: Testostérone (hormone male) et son rôle possible dans le traitement de certains cancers du sein. Acta Union Internat. contre cancer, 4: 377–382, 1939.

[36] Adair, F. E. and Herrman, J. B.: The use of testosterone propionate in the treatment of advanced carcinoma of the breast. Ann. Surg., 123: 1023–1035, 1946.

[37] Haddow, A., Watkinson, J. M., Paterson, E., and Koller, P. C.: Influence of synthetic oestrogens upon advanced malignant disease. Brit. M. J., 2: 393–398, 1944.

THE TREATMENT OF CANCER BY ENDOCRINE METHODS

The endocrine target cells are dependent on hormones for high metabolic activity and when deprived of this support pass into a lowered anabolic state. The new principles of medicine involved in the treatment of cancers by endocrine methods are two-fold. Cancers of endocrine target organs sometimes, and indeed frequently, retain sufficient of the characteristics of the normal cells from which they arose that they owe their activity to supporting endocrine substances; these are hormone-dependent tumors. This demonstration destroyed the universally accepted theory that cancer is an autonomous growth. Secondly, remote normal tissue which supports disease (here, cancer) need not operate at an abnormally high functional level; generally the stimulator operates at a normal or even a subnormal rate.

The mechanisms available for the control of dependent cancers are either to excise the source of the hormones maintaining the cancer and thereby forcing it to grow, or else to vitiate the physiologic effect of the cancer-supporting hormones by means of competitive inhibition.

Competitive inhibition between steroids has been known for about 17 years. Under certain circumstances the effects of administration of androgenic hormones may be prevented by the simultaneous injection of estrogen; in the rooster injected with estrogen, comb growth subsides to the height seen in castration. In the castrate fowl injected with androgen comb growth, vigorous in the controls, was inhibited[27] by estrogen. In the mouse the simultaneous injection of androgen with estrogen prevented[28] the development of squamous cells in the ventral prostate. Testosterone prevents estrus in the castrate rat injected with estrone[29] and metaplasia of the ventral prostate.[30] In the monkey[31] metaplasia of the prostate induced by estrogen is suppressed by androgen. In the dog[32] injected simultaneously with testosterone and diethylstilbestrol the prostatic secretion is reduced far below the output which follows androgen alone.

A partial solution to the therapeutic problem of control of cancer of prostate was provided with the demonstration that the *testis* often is the supporting factor maintaining this disease. Androgenic hormones stimulate the hormone-dependent prostatic tumors. They fail to cause exacerbation of prostatic cancer when it has lost so many of the qualities of normal prostatic epithelium that its metabolism

[27] Gley, P. and Delor, J.: Antagonisme entre la testostérone et la folliculine sur la crète du chapon. Compt. rend. Soc. biol., **125**: 813–815, 1937.

[28] Harsh, R., Overholser, M. D. and Wells, L. J.: Effects of oestrogen and androgen injections on reproductive organs in male rats and mice. J. Endocrinol., **1**: 261–267, 1939.

[29] Courrier, R. and Cohen-Solal, G.: Sur les rapports des hormones male et femelle testostérone et folliculine. Etude quantitative de leur antagonisme. Compt. rend. Soc. biol., **124**: 925–928, 1937.

[30] Korenchevsky, V. and Denison, M.: Histological changes in the organs of rats injected with oestrone alone or simultaneously with oestrone and testicular hormone. J. Path. and Bact., **41**: 323–337, 1935.

[31] Zuckerman, S. and Parkes, A. S.: Effect of sex hormones on the prostate of monkeys. Lancet, **1**: 242–247, 1936.

[32] Huggins, C. and Clark, P. J.: Quantitative studies of prostatic secretion: II. The effect of castration and of estrogen injection on the normal and the hyperplastic prostate gland of dogs. J. Exper. Med., **72**: 747–762, 1940.

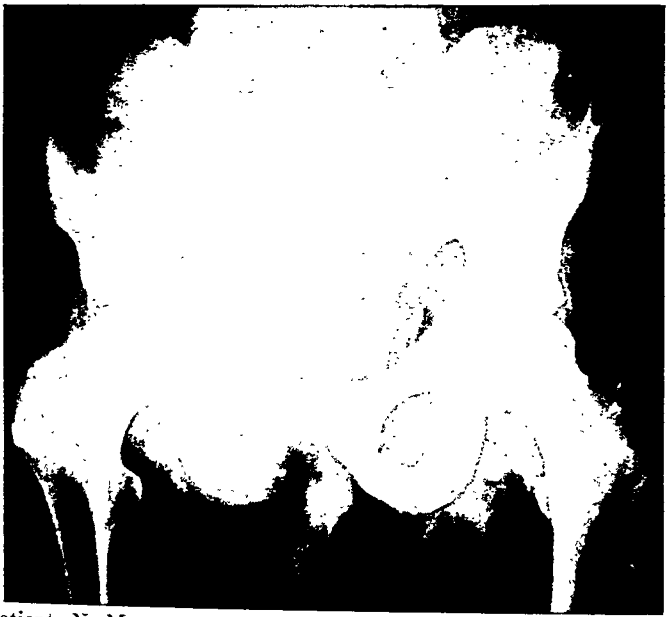

Fig. 3. Patient, N. M., age 63 years. Osteolytic metastases from cancer of prostate. Lesion was well controlled following orchiectomy in 1945, with estrogen administration for 4 years; since then progressive advance of lesion despite continuous administration of diethylstilbestrol.

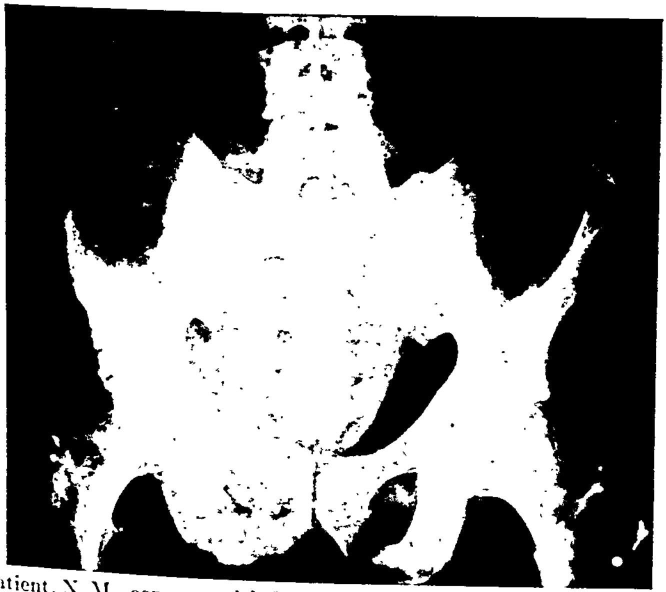

Fig. 4. Patient, N. M., compare with fig. 3. Conversion of osteolytic metastases to osteoblastic form 5 months following cortisone acetate, 50 mg. and diethylstilbestrol, 5 mg. daily; there was great clinical improvement on this regime.

duration of the remission. It is regretted that it is impossible to give the answers at this time. All that can be said is that certain cancers regress extensively and for many months, at least, when these little glands are excised; that therapy until methods had been devised for maintenance of human beings who are deprived of the adrenal glands by surgical operation. A method[38] for doing this was first found in 1945 when the maintenance relied principally on DOCA, plasma and salt. The procedure at that time was dangerous and life, although possible, was not good since the patient had signs of partial adrenal insufficiency with pigmentation and often anorexia; however some regression of the tumor was demonstrated.

With the availability of cortisone acetate in sufficient supply the clinical aspects of adrenalectomy were transformed.[39] Simultaneous bilateral adrenalectomy has now been done in 38 consecutive patients without fatality and with little morbidity. The surgical procedure is no longer perilous provided adequate surgical and chemical facilities are available.

"When maintained adequately adrenalectomized patients have a healthy appearance, are not incapacitated and they are able to engage in all their usual activities. Cutaneous pigmentation of the addisonian type does not occur. The patients withstand well the common ordeals of life. Under severe emergencies such as extreme heat and severe infection signs of adrenal insufficiency develop occasionally, but these are easily eliminated by increasing the amounts of cortisone acetate and DOCA."[40]

Despite the ease of maintenance of adrenalectomized man adrenal surgery must never be embarked upon lightly. The patient deprived of his adrenals will always develop an addisonian crisis when hormonal substitution is inadequate—when the amount supplied is less than the physiologic demand.

We have found [40] that certain patients with widespread cancer have an amelioration of the malignant process after adrenalectomy with maintenance on cortisone acetate. The remissions which occur are often brief and many patients are not benefitted in any way. Adrenalectomy had either no deterrent action or actually stimulated the growth of the following cancers (1 case of each kind): squamous carcinoma; melanosarcoma; chorionic epithelioma of testis; cancer of lung; cancer of stomach. In a man with chorionic epithelioma of the testis an associated gynecomastia of very high grade disappeared following the adrenalectomy regimen despite the rapid advance of the neoplasm.

Cancers which have responded have been neoplasms of the breast and prostate. The most favorable prostatic neoplasms have been of *category c* type.[40] The indications for mammary cancer are considered elsewhere.[41] In patients with far advanced mammary and prostatic carcinomas the improvement after adrenalectomy, when it occurs, may be profound and the clinical benefits quite impressive.

Many questions remain to be solved in the treatment of the appropriate cancers by adrenalectomy. It may well be asked what percentage of patients with far advanced mammary and prostatic cancers will respond and what is the

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[38] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic Cancer: Clinical features and urinary excretion of 17-ketosteroids and estrogen. Ann. Surg., 122: 1031–1041, 1945.

[39] Huggins, C. and Bergenstal, D. M.: Surgery of the adrenals. J. A. M. A., 147: 101–106, 1951.

[40] Huggins, C. and Bergenstal, D. M.: Inhibition of human mammary and prostatic cancers by adrenalectomy. Cancer Research, 12: 134–141, 1952.

[41] Huggins, C. and Dao, T. L. Y. Ann. Surg., in the press, 1952.

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ACUTE HYDRONEPHROSIS OF PREGNANCY

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It has been known for almost 200 years that the renal pelves and upper ureters of pregnant women are decidedly dilated.[1,5] For many years, speculation has been rife regarding the cause or causes of this phenomenon, originally ascribed to the pressure of the gravid uterus on the ureters as they cross the pelvic brim.

These changes in the upper urinary tract are found in 80 per cent or more of pregnant women.[2] They consist of dilatation of the renal pelves and of the upper two-thirds of the ureters, more marked on the right side, together with decreased peristalsis and decreased muscular tone of the ureters. This naturally leads to urinary stasis, which predisposes to infection. Indeed, pyelitis or pyelonephritis of pregnancy has been estimated to occur in from 10 to 60 per cent of pregnancies.[3] The physiologic, symptomless, "normal" dilatation of the ureters in pregnancy, with hydronephrosis, is not, of itself, of any particular importance, provided a) infection does not take place, and b) the ureter is not completely obstructed.

Much has been written regarding the changes of the urinary tract in pregnancy, the causes of these changes, and the effects.[4] As aforementioned, pressure of the uterus was at first thought to be the prime cause. That this thesis has merit is shown by the following facts:

1) Dilatation is practically always greater on the right side—due, probably to dextro-rotation of the uterus, and the presence of the sigmoid on the left side "protecting" the left ureter.

2) Ectopic (pelvic) kidneys and their ureters fail to show physiological dilatation of pregnancy.[6, 7]

3) The pelvic portion of the ureters does not participate in the dilatation of pregnancy.[8]

4) Eight different species of quadrupeds failed to show ureteral and pelvic dilatation.[9]

5) Acute hydronephrosis does occur, with *complete* obstruction of the ureter, undoubtedly due to the presence of the fetus in the gravid uterus[10, 11, 12] and the case herein reported.

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[1] Morgagni, J. B.: The Seats and Causes of Diseases (translated by B. Alexander). London: A. Millar, T. Cadell and Johnson and Payne, 1769, vol. 2, book 3, pp. 428–429. (Cited by Robertson, H. E.: Hydronephrosis and Pyelitis of Pregnancy. Philadelphia: W. B. Saunders Co., 1944.)

[2] Traut, H. F., McLane, C. M. and Kuder, A.: Surg., Gynec. and Obst., 64: 51–58, 1937.

[3] Strasberg, A.: Canad. M. A. J., 44: 24–26, 1941.

[4] Crabtree, E. G.: Urological Diseases of Pregnancy. Boston: Little, Brown and Co., 1942. (Bibliography list 2,160 titles.)

[5] Robertson, H. E.: Loc. cit.[1] (Over 900 references.)

[6] Everett, H. S.: Gynecological and Obstetrical Urology. Baltimore: Williams & Wilkins, 1944.

[7] TeLinde, R. W.: Am. J. Obst. & Gynec., 60: 273–284, 1950.

[8] Crabtree, E. G.: J. Urol., 38: 605: 619, 1937.

[9] Mengert, W. F.: Am. J. Obst. & Gynec., 27: 544–552, 1934.

[10] Strasberg, A.: Loc. cit.[3]

[11] Rabinowitsch, W.: Urol. and Cutan. Rev., 53: 81–83, 1949.

[12] Biskind, L. H. and Galvin, J. B.: Urol. & Cutan. Rev., 51: 495–497, 1947.

substituting for the presence of the adrenal is not difficult; and that the results in some cases are pleasing to the patient and gratifying to the physician.

Several new observations have been made concerning the therapy of advanced prostatic cancer with estrogenic and adrenal steroids: 1) Certain men with prostatic carcinoma, in relapse after the conventional anti-androgenic measures of orchiectomy and estrogen, may be benefitted by the combined administration of tablets of estrogen (diethylstilbestrol, 5 mg. daily) and cortisone acetate, 50 mg. daily; to increase the cortisone above this level does not seem to be wise. This steroid combination has given important relief (figs. 3, 4) to 2 feeble old men with large nodular primary prostatic growths (*category a*). 2) Following adrenalectomy with maintenance on cortisone acetate estrogens sometimes become effective therapeutic agents whereas previous to adrenalectomy they were ineffective.

SUMMARY

Endocrine-induced tumors of animals result from excessive stimulation of the hormonal targets. This can result from direct stimulation of a hormonal end organ or from failure of an inhibiting mechanism which may be conceived conveniently as a "closed cycle feedback". The evidence derived from experimentation reveals that not all endocrine substances are carcinogenic; endocrine carcinogenicity seems to be specific. The only hormones known to be carcinogenic are estrogens (of all kinds) and gonadotrophin. Known feedback sites whose absence causes cancers are the gonads and the thyroid.

When estrogen is a carcinogen its neoplasm-inducing properites are eliminated by testosterone. When gonadotrophin is a carcinogen, the tumors are eliminated by gonadal steroids.

Tumor maintenance may be independent of tumor induction with respect to endocrine substances. The hormones maintaining cancer may be of a different sort from those which initiated it. The elimination of steroid hormones from testis, ovary and adrenal causes regression, often of magnitude, of prostatic and mammary carcinomas when they are hormone-dependent neoplasms.

The oral administration of an estrogenic agent together with cortisone acetate occasionally will induce a remission in advanced prostatic cancers even when adrenalectomy is not done.

obstructed—apparently quite uncommon or unrecognized, and the subject of the case herein reported.

CASE REPORT

Mrs. M. V., a 19 year old gravida I, reported for obstetrical care in the fifteenth week of her pregnancy. The only positive findings were an accessory nipple on the left side at the level of the seventh rib. On the abdomen there was a well healed right paramedian appendectomy scar. A suprapubic mass extended 5 fingers above the symphysis. Pelvic examination showed a circumoral erosion of the cervix. The pelvis was judged to be adequate for vaginal delivery. Blood pressure was 102/60. The patient was a well developed and muscular female whose height was 4′11″, weight 129.

Urinalysis was negative for albumin and sugar, with a specific gravity of 1.024; microscopic findings were not remarkable. Hemoglobin was 14 gm. per 100 cc of whole blood. Papanicolaou smear of the cervix was negative. The chest film showed a "normal chest." Vaginal smears were negative for N. gonorrheae and Trichomonas vaginalis. The Mazzini floccculation test was negative. The patient's blood was group B, Rh positive. Her B.M.R. was plus 3. Her family and past history were noncontributory.

The prenatal course was uneventful at first, except for one episode of vaginal spotting which occurred at the eighteenth week of pregnancy.

During the twenty-ninth week of pregnancy, the patient was seen at home with a history of sudden sharp pain in the right flank radiating along the course of the right ureter. Temperature, pulse and respiration were within normal limits, and examination of the urine revealed numerous white and red blood cells. The impression was renal colic and a conservative regimen was begun. The next day the patient was seen again. The symptoms remained the same, and in addition to the signs of the right loin, she now had a temperature of 103F orally. She was thereupon hospitalized.

A urologic consultation was obtained. The impression was "renal colic, etiology to be determined."

The cystoscope was passed with slight difficulty, as the fetal head was pressing on the bladder. There was, however, no obstruction in the urethra. The bladder mucosa was congested; the orifices were in normal position. The right ureter was catheterized easily and the catheter passed for a distance of 30 cm. without obstruction. A hydronephrotic drip of clear urine was obtained, and 25–30 cc urine were aspirated from the right renal pelvis. Indigo carmine was injected intravenously and appeared in fairly good concentration in 15 minutes from both kidneys. A right retrograde pyelo-ureterogram was then done. This showed a point of obstruction where the backbone of the fetus crossed the ureter. Figure 1, *A* shows a film taken with the catheter still in the ureter. Figure 1, *B* shows the ureter and pelvis after the ureteral catheter had been completely withdrawn. A close look at figure 1, *B* will demonstrate normal ureter below the point of obstruction. Figure 1, *C* is the most interesting of all. This film, taken after the catheter and cystoscope had been withdrawn, and the patient having sat up for

However, that pressure is not the whole story is shown by the work of van Wagenen and co-workers[13, 14], who removed the fetus, but not the placenta, from pregnant rhesus monkeys, whose "pregnancy" continued to term. They found one of the following to occur, as shown by excretory urography:

1) Dilatation of the upper urinary tract *persisted;* or
2) Dilatation of the upper urinary tract *increased;* or
3) Dilatation, not previously present, appeared later on in the "fetus-less" pregnancy.

These changes were shown to regress normally after the placenta was delivered at term.

Traut and his co-workers[15] demonstrated decrease in the peristaltic activity and tone of the ureters in normal pregnant women. They suggested that the etiology of the ureteral atony was chemical (hormonal). As ureteral peristalsis decreased, the atony increased. Dilatation was at its maximum when the excretion of pregnancy hormone was at its peak. Beginning with the eighth calendar month, the process began to revert to normal, and normal conditions of the urinary tract were re-established by the seventh week post-partum. However, they believed that the increased weight of the pregnant uterus was undoubtedly a contributory factor.

It is interesting to note that van Wagenen and Jenkins[16] found, in rhesus monkeys, that pyelo-ureteral dilatation became less in successive pregnancies; also, MacLean and Deming[17] found that the incidence of pyelonephritis of pregnancy diminishes with each succeeding pregnancy. It is furthermore noteworthy that, as might be expected, when dilatation is at its maximum, the incidence of infection is greatest.

In summary, then, and without going into all the controversial features of this subject, we have the following factors at work to produce the physiological urinary changes of pregnancy (van Wagenen and Jenkins[13]):

1) Pressure of the gravid uterus at the pelvic brim.
2) Close application of the base of the bladder to the vagina and uterus.
3) Dextro-rotation of the uterus causes the right upper urinary tract to be more dilated than the left.
4) The left ureter is "protected" by the sigmoid colon.
5) Hormones of pregnancy cause atony of the ureters, with decreased peristalsis.
6) Lordosis of pregnancy may be a factor.

Whatever the causes may be, and however much each may play a part, the fact remains that the upper urinary tract *is* dilated and there *is* urinary stasis; this, as mentioned above, is not of particular significance unless infection sets in (pyelitis and pyelonephritis of pregnancy—quite common, and about which reams have been written), or the ureter is more or less *suddenly and completely*

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[13] van Wagenen, G. and Jenkins, R. H.: J. Urol., **42:** 1010–1020, 1939.
[14] van Wagenen, G. and Newton, W. H.: Am. J. Physiol., **129:** 485, 1940.
[15] Traut et al.: Loc. cit.[2]
[16] van Wagenen, G. and Jenkins, R. H.: J. Urol., **49:** 228–235, 1943.
[17] MacLean, J. T. and Deming, C. L.: J. Urol., **49:** 236–241, 1943.

Urine from the bladder showed 25–30 white blood cells per high powered field, and from the right kidney 6–8 white blood cells and 2–3 red blood cells per high powered field. Culture of the urine from the right kidney and bladder taken at cystoscopy was reported B. proteus. Four days later, catheterized bladder urine showed Strep. fecalis. Two days later, culture showed Escherichia, paracolon group.

Treatment consisted of postural drainage, with the patient lying on the unaffected side, and aureomycin by mouth. The temperature, which was 103.8F (rectal) on admission, became normal by the fourth hospital day. Urine obtained by catheter on the sixth hospital day was entirely negative. Excretory urography performed on the fourth hospital day after 3 full days of postural drainage. (fig. 1, *D*) showed a shift in the position of the fetus, and good function bilaterally. The patient was discharged on the eighth hospital day, afebrile, ambulatory and asymptomatic.

The remainder of her prenatal course was uneventful. She went into spontaneous labor the thirty-fifth week of her pregnancy and, after a total of 9 hours of labor, during which time the fetus's position changed from ROP to ROA, she was delivered of a 4 pound 10 ounce male by elective outlet forceps.

Urinalysis on this admission was negative. There was no urologic symptoms. She was discharged on the fifth post-partum day, after an afebrile, uneventful hospital stay.

Her course after leaving the hospital was without incident. Nine weeks after delivery excretory urography (fig. 2) was negative. The right kidney had returned to within normal limits.

A perusal of the literature reveals innumerable articles referable to urinary changes in pregnancy. However, we were able to find only 3 cases paralleling ours.

1) Strasberg[18] reported in 1941 a case of gross hematuria in a secundigravida, with pain in the right loin. This was shown to have been due to acute hydronephrosis, caused by obstruction in the midureter by pressure of the gravid uterus.

2) Biskind and Galvin[19] 1947, reported a case of recurrent left flank pain in a primigravida, which they believed to have been due to obstruction of the ureter by the fetus.

3) Rabinowitsch[20] in 1949, reported right renal colic, in a primigravida, which was caused by pressure of the uterus on the ureter.

In the case herein studied, and in the similar cases previously reported, there is a consistent pattern of events: Sudden onset of acute renal colic, plus or minus hematuria, in which, in most cases, the right side is involved; demonstrable occlusion of the mid-ureter, relief of which can be obtained either by ureteral catheterization and/or postural drainage, following which clinical symptoms, laboratory and x-ray findings regress.

There would seem to be no question but that in these cases the cause of the

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[18] Strasberg, A.: Loc. cit.[3]

[19] Biskind, L. H. and Galvin, J. B.: Loc. cit.[12]

[20] Rabinowitsch, W.: Loc. cit.[11]

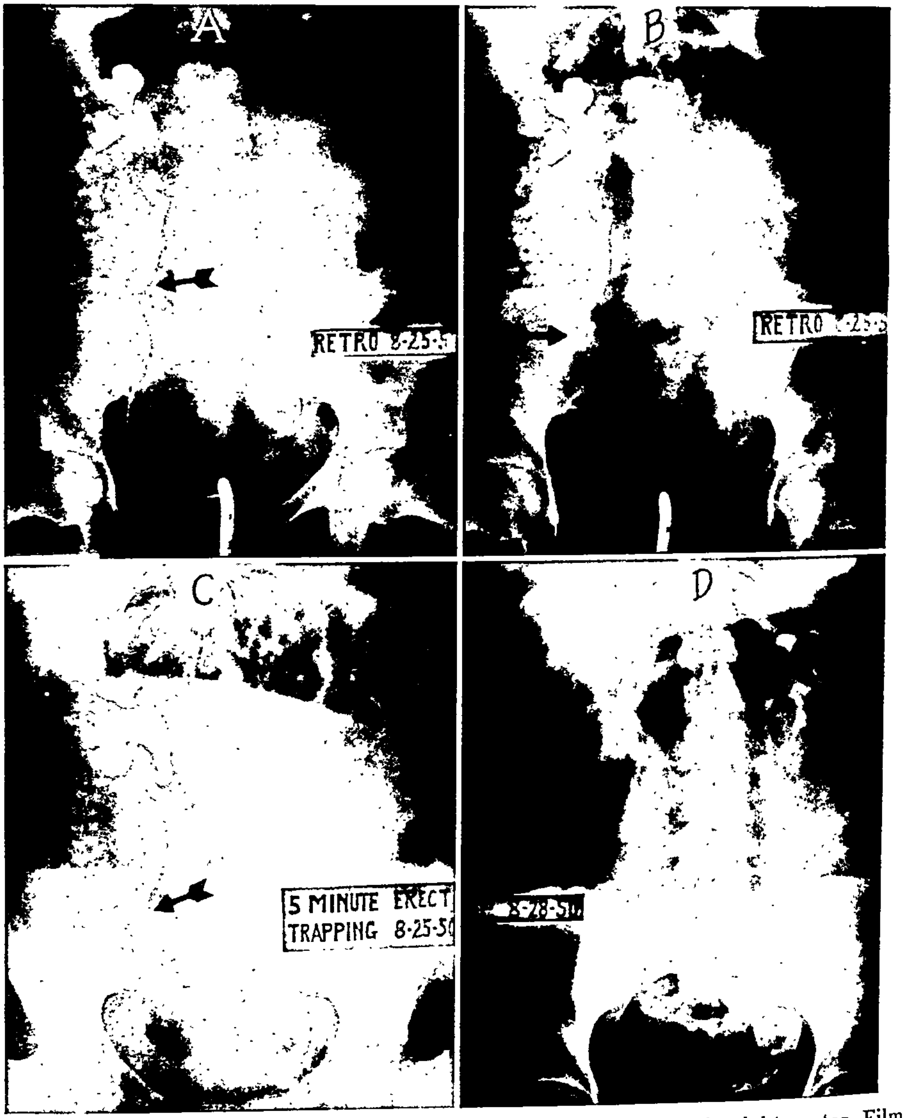

FIG. 1. *A*, retrograde pyelogram taken August 28, 1950. Catheter in right ureter. Film taken immediately after contrast substance had been injected. Note point of obstruction where backbone of fetus crosses ureter (arrow). *B*, film was taken as soon as ureteral catheter had been completely withdrawn. Patient still in supine position. Note point of obstruction (arrow) where fetus's backbone crosses ureter. In addition, close inspection will reveal lowermost portion of right ureter (superimposed over head of fetus, and below), which is perfectly normal. *C*, "trapping film," taken in erect position after cystoscope had been withdrawn and patient had sat up for 5 minutes. Point of obstruction, where backbone of fetus crosses right ureter (arrow) is well demonstrated. There is practically 100 per cent trapping indicating complete ureteral obstruction. *D*, excretory urogram taken after 3 days of "postural drainage" with shift in position of fetus. (Compare with *A*, *B*, *C*.) Physiological, normal dilatation of right urinary tract in pregnancy is well shown. On right side, hydronephrosis is present, somewhat more than is normally expected in pregnancy on right side. Patient asymptomatic at this time.

5 minutes, shows practically complete ureteral obstruction *apparently* by the pressure of the intrauterine fetus.

when indwelling ureteral catheter drainage was maintained for a prolonged period (3 months) for the treatment of pyelitis of pregnancy, and cited one case reported by Davidson[22] and one by Taylor[23]. Post-mortem studies revealed communication between the external iliac artery and the right ureter in Hamer's case. In the discussion of Hamer's case, it was pointed out that should ureteral catheter drainage be necessary, it would probably be best accomplished by a not-too-hard 5F ureteral catheter. However, it should be remembered that indwelling catheter drainage may introduce infection, where not previously present.

In 1939, Berkman and Priestley[24] described the "position-relief syndrome in hydronephrosis." Essentially this syndrome is that patients with uninfected hydronephrosis experience relief of symptoms by lying in certain positions, usually by lying on the unaffected side, thus promoting better drainage of the hydronephrosis. Although nothing about pregnancy hydronephrosis is mentioned in Berkman and Priestley's paper, it is significant that this method of position-relief has been used in pregnancy pyelitis and also in the acute hydronephrosis of pregnancy as described herein. In any discussion of pyelitis of pregnancy, it is important to bear in mind that pyelonephritis of pregnancy has been estimated to double the rate of fetal and maternal mortality, although these figures were obtained in the days before antibiotics (Bowen and Stites[25]). With proper and adequate diagnosis and therapy, this should no longer obtain.

CONCLUSIONS

Dilated ureters and pelves are found in almost every pregnancy and are considered "physiological."

On the other hand, acute hydronephrosis of pregnancy, secondary to ureteral occlusion caused by the gravid uterus, is a definite pathologic entity.

Acute hydronephrosis of pregnancy should be suspected when there is renal colic and/or hematuria. It is easily diagnosed by recourse to excretory urography, and/or retrograde pyelography with trapping films.

Treatment is best accomplished by position or posture-relief, most always by lying on the unaffected side. Indwelling ureteral catheter drainage is not without danger—it may contribute to renal infection, or may in some instances, cause alarming, even fatal, hemorrhage.

The use of appropriate chemotherapy and antibiotics is recommended to combat urinary tract infection. Adequate drainage is a sine qua non in treating urinary tract infections.

A plea is made for close co-operation between the obstetrician and the urologist in the care of urologic disease of pregnancy.

Finally, as Crabtree and others have pointed out, the ability and the tendency for the urinary tract changes of pregnancy to retrogress following delivery, make for an attitude of conservatism in therapy.

[22] Davidson: Cited by Hamer.[21]
[23] Taylor: Cited by Hamer.[21]
[24] Berkman, J. M. and Priestley, J. T.: Minnesota Med., **22**: 217–222, 1939.
[25] Bowen, J. A. and Stites, J. R.: South. Med. J., **34**: 494–497, 1941.

acute ureteral obstruction was extrinsic pressure by the gravid uterus. It would appear that firm abdominal musculature may play a secondary role in the compression of the ureter by the uterus.

Although much has been written about dilatation of the upper urinary tract in pregnancy, and about pyelitis of pregnancy, and both are well recognized, we feel that more recognition should be accorded the entity of acute hydronephrosis of pregnancy due to ureteral occlusion by the gravid uterus. *Acute* hydronephrosis of pregnancy would appear to be a neglected field of study. The major texts on obstetrical urology (Crabtree[4], Robertson[5], Everett[6]) do not discuss this syndrome which we believe is a definite pathologic entity, in contradistinction to the normal physiologic ureteral and pelvic dilatation of pregnancy. Adequate study of the urinary tract by obstetricians and urologists during pregnancy would undoubtedly reveal more of the fundamental changes of ureteral occlusion.

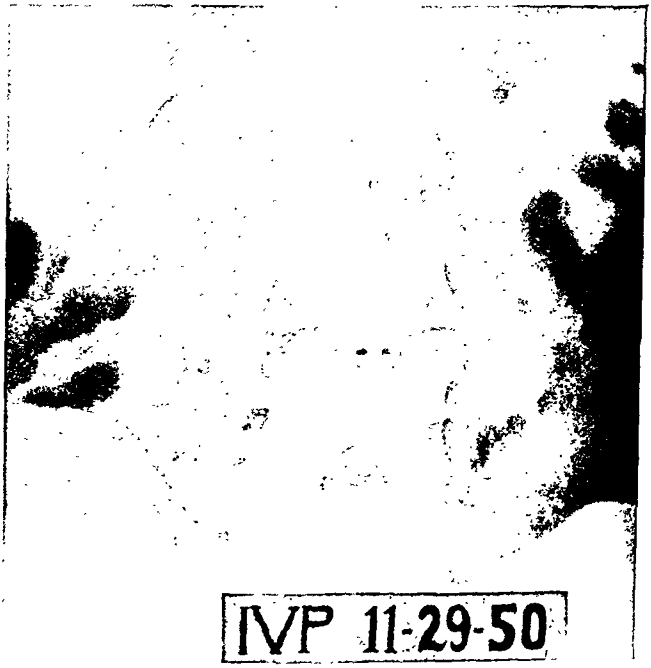

FIG. 2. Excretory urogram taken November 29, 1950, three months after acute episode of hydronephrosis shown in figure 1, *A*, *B* and *C*, and 9 weeks after spontaneous delivery of infant. Right hydronephrosis has disappeared following delivery, and kidney has returned to normal. Left kidney, not well shown, is normal.

Relief of the obstruction can be accomplished by "postural drainage," as in the present case, or indwelling ureteral catheter drainage. The latter, although effective, may be dangerous especially if done for a prolonged period. Hamer[21] reported a case of fatal hemorrhage due to erosion into the iliac artery occurring

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[21] Hamer, H. G.: Tr. Am. A. Genito-Urin. Surg., 32: 177-183, 1939.

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OCCULT CARCINOMA IN CLINICALLY BENIGN HYPERTROPHY OF THE PROSTATE: A PATHOLOGICAL AND CLINICAL STUDY

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Carcinoma within benign hypertrophy of the prostate gland has long been known to occur. The frequency of such a finding has been estimated to be small. In recent years, however, more careful investigations and more detailed studies have demonstrated that such an occurrence is much more frequently seen than was previously surmised (table 1). Our study covers a series of cases wherein the prostate was found to be clinically benign. In addition to this investigation we have followed up another group of patients who prior to our present study had undergone a suprapubic operation for supposedly benign hypertrophy and whose specimens had revealed the presence of carcinoma histologically.

Hirsch and Schmidt state that small carcinomas of the prostate with or without metastases, especially to bones, are not unknown. Such growths have a certain clinical importance because they are concealed in tissues removed surgically for the relief of symptoms caused by enlargement of the prostate and are so small or have produced so little change as to escape notice when the gland is examined grossly. Their presence is demonstrated only by microscopic examination. Hunt comments that there is a borderline group of cases in which clinical distinction between benign and malignant disease is impossible and only through the study of sections from specimens obtained at operation or necropsy may the accuracy of diagnosis be established. Bell states that only about 10 per cent of carcinomas give a long history of simple hypertrophy, but on the other hand adenomas are present in the large majority of the carcinomatous glands.

According to Dossot, prostatic adenoma plays an important role in the pathogenesis of cancer, in 11.6 per cent of the cases the adenoma undergoes malignant degeneration. Of 75 cases of apparently benign prostatic obstruction analyzed by Myers, in which there was no clinical evidence of carcinoma, and which were operated either by the suprapubic route or by the cautery punch resection, 29.4 per cent revealed evidence of malignancy.

In a pathologic study of 490 prostates which were diagnosed nonmalignant both clinically and on routine macroscopic and microscopic post-mortem examination, Kahler by further examining sections of these glands, found 54 (11 per cent) cases of carcinoma. Barringer reported carcinoma in 17.4 per cent of prostates showing adenomatous hyperplasia. In a review of 108 cases in which suprapubic operation was performed, Treiger et al. found malignancy of the prostate in 12.6 per cent of the cases.

There are two schools of opinion as to the relationship of the adenoma and the carcinoma in the prostate. Most of the French authors believe (summarized by Dossot) that the peri-urethral adenoma frequently undergoes cancerous degeneration and that one finds numerous intermediary stages between benign and malig-

SUMMARY

A case of acute hydronephrosis of pregnancy due to ureteral occlusion by the gravid uterus is presented, together with summaries of previous similar cases. We believe that this is a definite clinical entity, hitherto given little emphasis in texts.

The physiologic and pathologic obstructive urinary tract changes of pregnancy are briefly discussed, with a consideration of the etiology, diagnosis, therapy and prognosis.

99 Pratt St., Hartford 3, Conn.

On histologic examination, nine of the 98 cases revealed malignant tissue (9.2 per cent). The age distribution was as follows: 4 in the seventh decade, 3 in the eighth decade and 2 in the ninth decade. The presenting complaint in 3 cases was acute retention of urine, hematuria in 1 case, and frequency and nocturia in the remaining 5 cases. The gland was classified for size as grade 2 in 3 cases, grade 3 in 3 cases and grade 4 in 3 cases. The weight of the enucleated specimens averaged approximately 40 gm.

Table 2 shows the part of the specimen in which the malignant areas were found.

The specimens obtained from H. S. and L. L. were extensively involved by carcinoma. H. L. showed one small area of malignancy, but within 1 year he had a recurrence of urinary difficulty, and x-ray studies revealed metastases to the spine. He underwent three transurethral resections for the relief of the obstruction. A bilateral orchiectomy was done and he received female sex hormone. He expired 2 years from the date of the initial operation.

TABLE 2

CASE	CENTER		PERIPHERY	
	Right	Left	Right	Left
J. F.	×	×	×	×
L. S.		×		×
H. S.	×	×		×
L. A.	×	×		
J. R.		×		
L. L.	×	×	×	×
H. L.			×	
J. G.		×		
S. B.				×

A separate study, as stated, was undertaken to ascertain the status of a group of patients who had undergone suprapubic operation for benign hypertrophy and in whom microscopic carcinoma had been found. A total of 49 such patients had been seen at the Mount Sinai Hospital from 1930 to 1948. In the follow-up study we obtained meaningful information in 41 cases. Eight cases could not be traced. Our findings revealed that 29 patients (71 per cent) are still alive and 12 have died. The death group of 12 consisted of 4 who died in the hospital immediately after surgery, 7 who lived over 5 years and died from natural causes, and 1 who lived 2 years and expired from chronic lymphatic leukemia. Of the 29 living patients, 21 (72 per cent) have passed the five year mark.

Of the entire group of 41 cases, in only 3 cases did metastases develop.

These findings are interesting in that they show that by a clean enucleation of the hypertrophied portion of the gland, most of these patients had no recurrence of the carcinomatous process observed histologically. Unquestionable metastases developed in only 3 of the 41 cases. Such a salvage is noteworthy and speaks favorably for enucleation. This is especially notable when one considers the fact that the first part of this study has demonstrated the variable sites of distribution of the occult carcinoma in the clinically benign hypertrophied prostate.

nant lesions. Conversely most of the American authors believe that the adenoma and the cancer co-exist, but have an origin entirely distinct; that cancer developing in the prostate only secondarily invades the peri-urethral adenoma in the *same manner as it spreads to neighboring organs. Barnes et al.*, in a histo-pathological study of prostatic tissue, state that cancer of the prostate was often associated with benign hypertrophy of the gland. He asserts that when carcinoma was associated with benign hypertrophy, they represent islands of malignancy isolated form, though surrounded by, adenomatous formations. Moore, in a morphological study of benign hypertrophy of the prostate, observes that carcinoma developing in a nodule of benign hypertrophy without involvement of the surrounding prostatic tissue was rare. When carcinoma was present in both the areas of benign hypertrophy and the contiguous prostate no conclusions in regard to its origin was possible. Since, in the American opinion, carcinoma of the prostate rarely occurs in acini already hyperplastic and involved in benign enlargement, it follows that the carcinoma which arises in a gland also the seat of benign hypertrophy is not taken to be related to the latter.

TABLE 1

AUTHOR	PER CENT	MATERIAL
Bell	15.0	Autopsy
Dossot	11.6	Surgical and autopsy
Myers	29.4	Surgical
Kahler	11.0	Clinical and autopsy
Barringer	17.4	Clinical
Treiger et al	12.6	Surgical
Moore	16.7	Autopsy

Our study consisted of a microscopic investigation of 98 consecutive cases of prostatic hypertrophy, which were diagnosed clinically as nonmalignant. All these cases were operated upon by the suprapubic approach. In order to obtain a section from every part of the specimen, it was sectioned according to a definite plan. The specimen was divided into right and left halves. Each half was then subdivided into upper and lower and further divided into anterior and posterior parts. In that manner we were certain of obtaining sections representing the entire specimen. All sections were processed alike and stained with hematoxylin and eosin.

Of the 98 subjects operated upon, 97 patients were white and one was colored. They ranged in ages from 44 to 95 and were in the following decades.

	DECADES					
	5th	6th	7th	8th	9th	10th
No. patients	2	18	50	18	9	1

Preoperative x-ray studies revealed the absence of metastases. The prostate by rectum felt benign and the serum acid phosphatase determinations were within normal limits.

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ADENOCARCINOMA OF THE COLON WITH PRIMARY COMPLAINT OF TUMOR OF PENIS; REPORT, WITH CONSIDERATIONS OF MODE OF OCCURRENCE

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Secondary involvement of the penis by a primary malignant tumor of another organ is a rare occurrence. In many such cases, with neoplastic infiltration of the corpora cavernosa, the first symptom is priapism. The priapism is not necessarily due to direct neoplastic invasion of veins, but may be due to stasis and/or thrombosis.

Several cases of cancer metastasizing to the penis from other organs (bladder,[1-5] prostate,[6-12] testis,[13-15] kidney,[16, 17] liver,[18] lung,[19] and 'angioendothelioma' of the ilium[20]) have been published. The area of the sigmoid colon and rectum is a very frequent site of carcinoma, but it is well known that local retrograde metastases do not frequently occur more than 1–2 cm. from the primary, and that distant retrograde metastases are rare. Specifically, retrograde metastasis from sigmoid colon or rectum to penis is a rarity that has been reported only 4 times previously,[21-24] and in none of the reports was there any generally satisfactory elucidation of possible modes of origin of this seemingly curious pattern of spread. There follows a report of a man who came to the outpatient clinic because of lumps on his penis; later only was the primary rectosigmoid carcinoma found.

CASE REPORT

J. L. P., (BFS&CH) No. 88147), a 68 year old white farmer from Arkansas, was first seen in the outpatient clinic on July 29, 1942, complaining of several

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* Work done while trainee, National Cancer Institute.

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SUMMARY

We have studied histologically 98 cases of clinically diagnosed benign hypertrophy of the prostate, recently operated upon suprapubically. This study disclosed 9.2 per cent of co-existing carcinoma. These carcinomatous areas did not show any predilection for any specific area of the specimen.

An older similar series of 41 cases of occult carcinoma has been investigated by follow-up. Of these, 12 have died of causes apparently unrelated to carcinoma of the prostate. Of the remaining 29, three showed present evidence of metastases from the primary site.

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hard mass, 2 cm. across. Microscopic examination showed adenocarcinoma, the source of which was not clear. Figure 1, *A* and *B* show the microscopic appearance.

On August 12, 1942 the patient entered the hospital. More detailed history revealed that 2 months prior to admission he had discovered a lump at the base of the penis on the dorsal aspect. This had rapidly increased in size and during the past month had become painful. Since appearance of the first growth at the base of the penis, three other lumps had made their appearance on the dorsum of the shaft near the glans and these had been present about one month. At about this time bilateral enlargement of the inguinal nodes was noticed. There was no history of trauma or bleeding.

Past history was pertinent in that he told of a white, painless penile lesion occurring at the age of 39 years. A physician had diagnosed this as syphilitic (by inspection) and had administered two intravenous injections of '606'. No serologic test for syphilis had ever been made.

In this system review the patient stated that during the year prior to admission he had had low abdominal cramping which had increased in severity recently. Constipation had been noticed during this year's time and had become an obstipation by the time of admission. There had also been slight rectal bleeding accompanying defecation in this period. Recent genito-urinary history revealed increasing nocturia in the past 3 months, with micturition from 3 to 8 times a night associated with increasing dribbling. There was no dysuria or hematuria. The patient gave a history of weight loss (15 pounds) in the past year.

Physical examination showed a wasted, moderately chronically ill male in no acute distress. Vital signs were normal excepting that the blood pressure was 210/110. Lung fields were clear with questionable sticky rales in the low hilar regions, thought by the examiner to be within normal limits. Cardiac dulness to percussion was increased to the left. Cardiac rhythm was regular; heart sounds were slurred with a soft systolic apical murmur. The abdomen was flat and soft, with slight low abdominal distention. The liver edge, felt 2 cm. below the costal margin, had a moderately firm consistency and was smooth.

Examination of the genitalia showed the presence of a firm mass almost surrounding the base of the penis and displacing it posteriorly. Other smaller, hard nodules were present along the shaft on the dorsal aspect, the largest measuring 1.5 cm. in diameter. Ulceration was not noted. Priapism was not present. The scrotum and testes were normal. Bilateral hard inguinal lymph nodes measuring up to 2 cm. in diameter were palpable. Rectal digital examination found, in the uppermost part of the rectum, the lower edge of an ulcerating mass. The rectal mucosa just cephalad to the prostate was normal.

The routine laboratory examinations of the blood and urine were normal except for a leukocytosis of 13,550 mm. The Kahn test was negative. Acid phosphatase was reported as within normal limits.

It had become evident that the patient had an advanced carcinoma at the level of the rectosigmoid with retrograde penile and inguinal metastases. By way of additional confirmation proctoscopic examination was followed by barium *nodules on his penis. These had appeared within the previous 2 months* and had become painful. There were enlarged, hard inguinal lymph nodes bilaterally. Because the initial impression was carcinoma of the urethra with inguinal metastases, one of the left inguinal nodes was removed for biopsy and the patient was given a reservation date to enter the hospital.

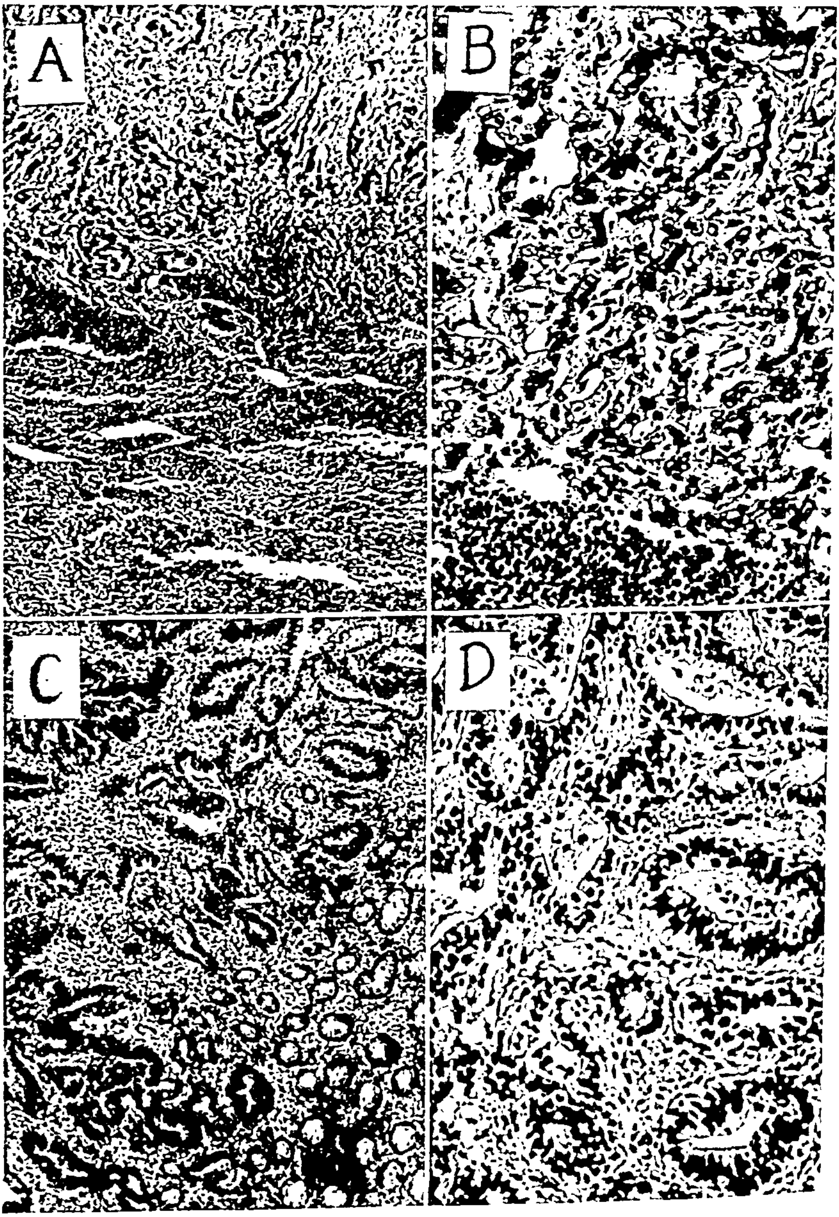

FIG. 1

Gross examination of the lymph node (BFS&CH Acc. No. 42-962) showed a of the penis, in regions where tributaries to the dorsal vein flow. The tumors are multiple and have been described usually as occurring in a line along the dorsal vein. An analogous occurrence might be expected in the female, and at least one case with metastases to the vulva from carcinoma of the rectum has been described.[25]

Stein and Hantsch[23] have explained retrograde spread from rectum to penis as being due to direct extension into the corpora cavernosa by way of the ischiorectal fossa, thence through the junction of the deep and superficial triangular ligaments with Colles' fascia into the superficial perineal space. While this could be the manner of spread from a low-lying rectal tumor, the position at the rectosigmoid as in the present case seems too high for a direct extension, and none was detected. A much more likely explanation of the spread in this case, as well as in several of the cases gathered from the literature, would appear to be found in the following considerations:

1) The monumental work of Batson[26] in 1940 has contributed to an understanding of retrograde spread, either of tumor or of infection, to the penis. By the injection of a radiopaque artists' water color solution, under low pressure, into the dorsal vein of the penis, Batson demonstrated repeatedly the vast intercommunication system between the pelvic and the vertebral veins. The experiments were done with male human cadavers and anesthetized Macacus Rhesus monkeys. It was seen that the connections and collateral circulation of the dorsal vein of the penis are the same as those of the prostatic plexus with which it connects. The valves in these veins are exceedingly variable, and permit flow toward the sacral plexus. Showing the wide range of the injected dye fluid, one could follow the medium, fluoroscopically, entering the lateral sacral veins, into the veins of the sacral canal and the wings of the ilia. The medium could be followed up the entire vertebral plexus, into intercostal veins, and even on into the cranial vault.

Batson's results clearly help to explain many otherwise bizarre osseous metastases from prostatic carcinoma (see also, however, Willis,[27] p. 592); that they are of assistance in the present case may become evident directly.

2) While there seems to be no constant direct connection between the portal drainage of the rectosigmoid area and the pelvic veins, occasional communications and variations in the venous system which could allow such a retrograde metastasis as from the lower colon to the penis have been demonstrated often, and are recorded by anatomists in standard works.

3) During the Valsalva maneuver (coughing, sneezing, straining at stool, etc.) blood may be squeezed from intra-abdominal veins into the vertebral system. Since the vertebral system is one of low pressure and apparently reversible flow, this fact coupled with those set forth above offers logical explanation for such metastases as occurred in the present case. One might, indeed, wonder why their occurrence is not more frequent.

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enema. The proctoscope was easily introduced and passed for a distance of 15 cm. where a distinct obstruction was met. An ulcerating, friable, bleeding mass was seen. Biopsy (BFS&CH Acc. No. 42-1019) was taken from this mass, and reported as adenocarcinoma of the rectum (fig. 1, *C* and *D*). Roentgenographic studies showed a filling defect with constriction of the sigmoidal lumen.

Because of the apparently hopeless prognosis, palliative colostomy was thought advisable, so preparation by repeated enemas and oral sulfasuccidine was begun. On August 26, 1942 a left paramedian abdominal incision was made. General exploration of the abdomen revealed no palpable liver metastasis, but a hard nodular mass, about 2 cm. in diameter, was felt in the region of the right crus of the diaphragm, and this was thought to be an evident metastasis. The distal half of the colon contained an unusually large amount of inspissated feces, due to the almost completely obstructing lesion, and the splenic flexure was almost sausage-like. When the redundant sigmoid was elevated a large tumor mass at the rectosigmoid, extending through the bowel wall, was visualized, but there was no attachment to other viscera. Because of the impacted feces proximal to the tumor a cecostomy was done. The general postoperative course was satisfactory, the cecostomy stoma being gradually dilated to allow repeated enemata, which gave fairly good returns. At the time of the exploratory operation a large biopsy was taken from one of the penile nodules, and this also showed adenocarcinoma (BFS&CH Acc. No. 42-1082, fig. 2).

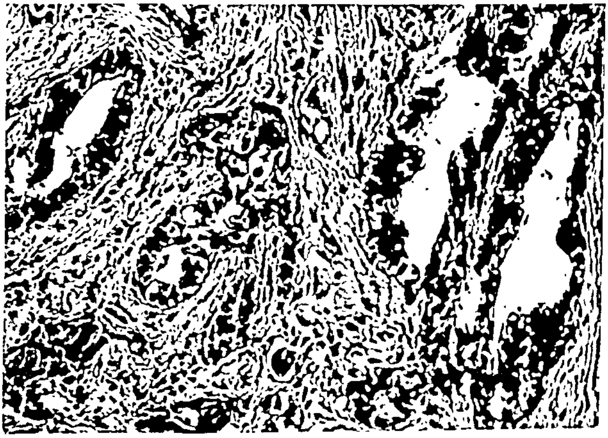

FIG. 2

Since it was believed that nothing further could be done for the patient, he was permitted to go home on the twenty-first postoperative day. His condition rapidly deteriorated, and he died at home, October 9, 1942, according to a note from his physician.

DISCUSSION

A pattern exists in the distribution of penile metastases from other abdominal organs. The secondary tumors have most frequently occurred on the dorsal aspect

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PHALLOPLASTY

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Plastic reconstruction of the penis after traumatic or surgical amputation has been reported by Bogoras (1936), Frumkin (1943–44), Bergman et al. (1948), and Henninger (1951). These authors have used abdominal tube flaps reinforced with rib cartilage and attached them to the penile stump in staged operations. They constructed the urethra either from a free split-thickness tube graft or by using skin from the new phallus. Bergman et al. made the urethra from the inferior portion of the new penis and then covered the defect with scrotal skin using the Wehrbein procedure.

This paper is to report a new, simple technique in which the scrotum is used to construct both the urethra and the new penis in direct continuity with the stump. The operation is applicable in any case where the urethral meatus is anterior and superior to the scrotum after amputation. It would not be possible in a case with permanent perineal urethrostomy. It should be reserved for adults where the scrotum has reached its maximum growth. It has been employed successfully in two cases after surgical amputation of the penis for malignancy.

SURGICAL TECHNIQUE

The plastic reconstruction may be undertaken at some time after the wounds of amputation are completely healed and the tissues are free from edema; or, as in case 2, the first stage may be done at the time of amputation if infection is not a factor.

First stage. After meticulous cleansing of the scrotum and perineum, the urine is diverted by temporary perineal urethrostomy and an indwelling catheter. (Cecil.) The new urethra is constructed from midline scrotal skin using a Thiersch-Duplay technique (fig. 1). A racquet shaped incision is made around the urethral meatus at the penile stump, and the distal ends of the incision are extended in two parallel lines 15–20 mm. apart down the full length of the scrotum where they are joined by a right angle transverse incision. These cut edges are then approximated over a catheter with continuous 00000 chromic catgut to form the new urethra which is continuous with the old meatus. The new meatus now lies at the bottom of the scrotum. The remaining scrotal skin edges and abundant fasciae are undermined and approximated in two layers over the new urethra which then lies buried in the scrotum. Interrupted fine plain catgut is used for the fascial layer, and the skin is closed either with interrupted silk or silver wire sutures. Antibiotics are used postoperatively. As noted elsewhere (Goodwin and Thelen) in employing scrotal skin to cover a denuded penis, the abundant blood supply and excess tissue of the adult scrotum make for rapid healing and ease of operation. The urethrostomy catheter is removed on approximately the tenth postoperative day. Soon thereafter the patient may leave the hospital voiding through the new urethra at the bottom of his scrotum. The exact midline scrotal

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Read at meeting of the Los Angeles Urological Society, April 1, 1952

SUMMARY

An unusual case of retrograde metastasis from an adenocarcinoma of the recto-sigmoid area to the penis, the fifth in world literature, has been reported.

The method of spread is believed to be through the vertebral veins.

Anatomic and physiologic considerations held to be of importance in elucidating the happenings in this case, and similar cases, are presented.

ADDENDUM

Since our manuscript was submitted, Cattell and Mace (J.A.M.A. **146:** 1230, 1951) have reported a case of rectal carcinoma with metastasis to the penis, the patient being a 9-year reclaim after removal of his tumors. Thus, our case is numerically the sixth of its sort.

Veterans Administration Hospital, San Francisco 21, Calif. (J. B. F.)

The use of splints. Bergman et al. (1948) and Bett (1951) have described and discussed nature's use of the baculum or os penis to assist in erection. All the authors who have written on plastic reconstruction of the penis have used cartilage implants to produce rigidity in their cases. In one of our cases rib cartilage was used unsuccessfully due to curvature of the cartilage graft (case 2). In case 1 an attempt was made in the first stage to produce a large splint with an implant of acrylic. This later had to be removed because it was too large and produced a pressure defect and draining sinus.

Implanted acrylic prostheses have been successfully used elsewhere in the body, however, (Rea, 1943; Holt and Lloyd, 1948; and Judet, 1950), and it may be that properly shaped splints of acrylic can be successfully employed as an artificial baculum in these cases. In our experience, four other patients have had penile implants of acrylic splints for other reasons (one after excision of the urethra and corpus spongiosum for tumor, and three* in an attempt to provide partial erection for the complaint of impotence). Two of these patients have tolerated the acrylic splints well for over two years. In the other two cases the splints had to be removed because of the patient's intolerance to them although there was no evidence of unfavorable tissue reaction or damage.

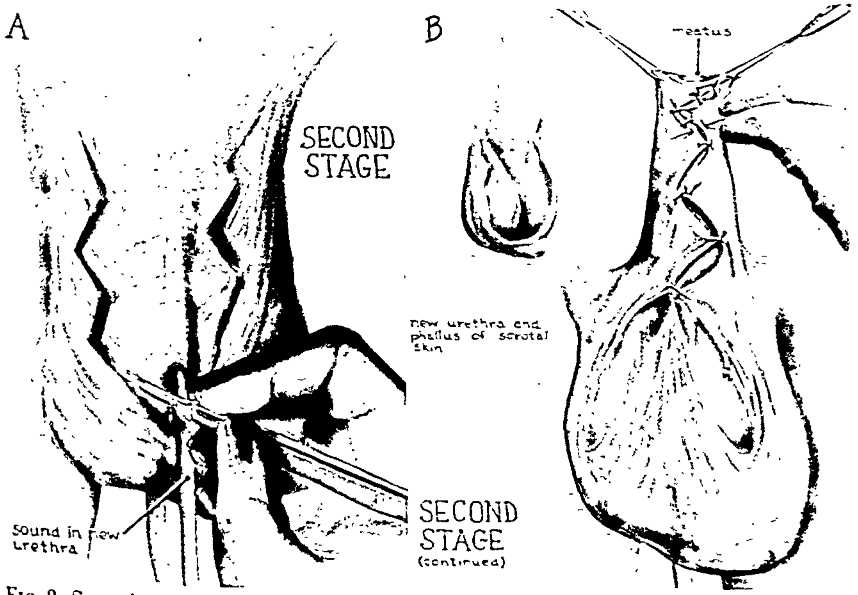

Fig. 2. Second stage. *A*, incisions are made on each side of scrotum to free scrotal skin and deep fasciae which will form new phallus. *B*, freed midportion of scrotum, containing new urethra, is lifted upward. Ventral edges of this bulk of tissue are approximated.

As demonstrated so well in the cases of Borgoras and of Bergman et al., an artificial splinting effect of some sort is necessary if the new phallus is to serve for anything more than a waterspout or decoration.

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* The first of these was a case treated by Dr. Peter L. Scardino after traumatic spinal injury and impotence.

skin is nearly hairless, and hair in the new urethra has not yet been a problem in these cases.

Second stage. Several weeks or months later, after all edema has subsided and healing from the first stage is complete, the second stage is undertaken. Warming the scrotum helps to produce maximum relaxation of the cremaster. A Foley catheter is inserted through the new urethra into the bladder and left in place. The second stage closely resembles the second stage of Cecil's operation (1946).

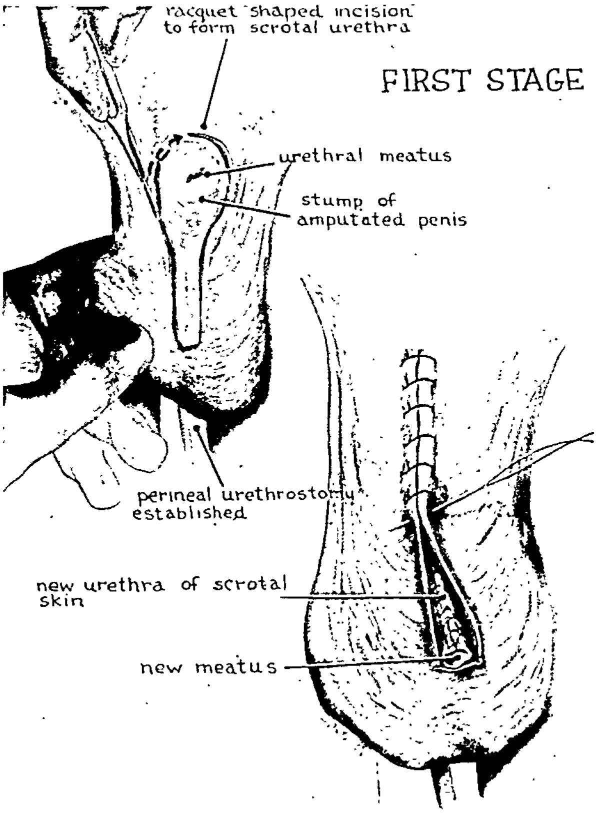
racquet shaped incision to form scrotal urethra
FIRST STAGE
urethral meatus
stump of amputated penis
perineal urethrostomy established
new urethra of scrotal skin
new meatus

FIG. 1. First stage. New urethra is constructed from midline scrotal skin using Thiersch-Duplay technique. New urinary meatus now lies at bottom of scrotum.

Parallel or staggered zig-zag incisions are made on each side of the scrotum lateral to the urethra and at least 8 to 10 cm. apart (fig. 2, *A*). These extend from the base of the penis down to the bottom of the scrotum where the new urethral meatus is lifted free from its attachment to the rest of the scrotum. The incisions are extended through the subcutaneous fasciae and deeper to include some of the redundant muscular and areolar tissue of the scrotum. The cords and testes may be exposed (fig. 2,*B*, inset). The freed midportion of the scrotum, containing the new urethra, is lifted upward. The ventral edges of this mass of skin and tissue are then approximated with silver wire sutures to form the new phallus (fig. 2,*B*). The scrotal defect is easily closed in two layers because of the excess skin.

in figure 3 taken when the patient returned for stage 2, two years later. The new urethral meatus lay at the bottom of the scrotum, and the patient was able to void well in the sitting position without soiling his clothes, but he desired and requested the final stage. This was carried out, as described and illustrated, on March 9, 1951. The satisfactory cosmetic appearance and functional end result as far as urination is concerned are seen in figure 4. The need of a splint at his age is slight and no further treatment is contemplated.

Case 2. L. S., J. H. H. No. 292,636, B. U. I. No. 33553, a 27-year-old white man, had simple amputation of the penis for a peculiar malignant tumor, probably fibrosarcoma, on October 12, 1949. At the same time, using the experience gained from case 1, the first stage phalloplasty was performed as described previously. In this instance, however, the freshly cut end of the urethra after amputation was anastomosed directly to the new distal urethra made of scrotal skin. Fine chromic catgut sutures were used, and the approximation was made over a splinting catheter which was later removed. The postoperative course was uneventful.

On November 30, 1949, the second stage operation was performed as described. Vertical instead of zig-zag incisions were used in freeing the new penis from the scrotum.

Because the patient was young and desired to marry, it was decided to attempt to produce rigidity of the new phallus with a rib cartilage graft. This was done January 24, 1950, with good immediate result. However, when most recently seen in April 1951, he complained that the cartilage had curved on itself and no longer served its purpose as a baculum. Removal and replacement of the present cartilage graft is contemplated.

DISCUSSION

The plastic reconstruction of an amputated penis has limited application. However, for the patient concerned it may be a matter of greatest importance regardless of age. The young man may wish a sexually potent organ as well as a waterspout. The old man may desire decoration—and the comforts of a conventional external urinary apparatus. A simple method of phalloplasty, which can be offered the potential amputee at the time penile amputation is proposed, may help to soften the blow of such a proposal.

SUMMARY

A new method of plastic reconstruction of the penis after amputation is presented. The two stage phalloplasty utilizes scrotal skin for the urethra and all layers of the scrotum in creating the penis. The use of splints of cartilage or acrylic is briefly discussed.

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CASE REPORTS

Case 1. W. K., J. H. H. No. 396,148, B. U. I. No. 39423, a 76-year-old white man, underwent Young's radical amputation of the penis for carcinoma in August 1946. The resulting short stump and urethra flush with the abdominal wall and top of the scrotum proved troublesome to the patient who found it difficult to void without wetting his clothing. On February 7, 1949, the first stage phalloplasty was carried out as described. The already mentioned addition of an acrylic splint at the time of the first stage proved unsatisfactory, and it had to be removed 2 months later. The excellent late result of this first stage operation is seen

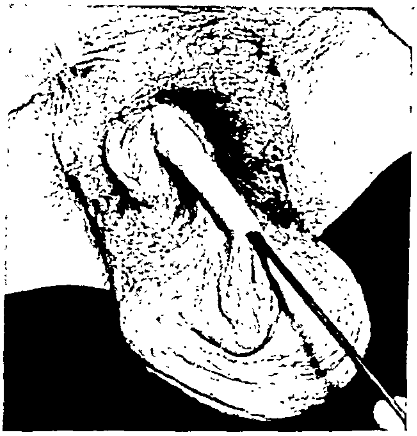

FIG. 3. Case 1. After first stage phalloplasty. Note short penile stump and urethra formed from scrotum with the new meatus at the bottom of the scrotum. (Compare with figure 1.)

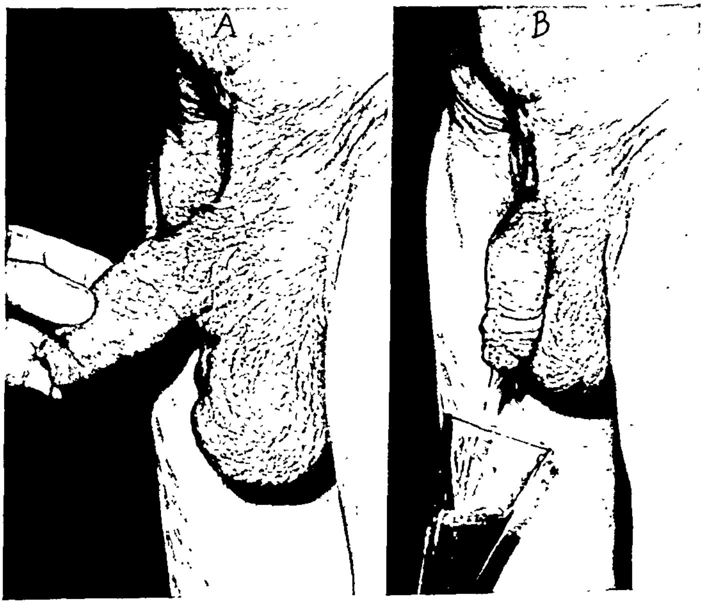

FIG. 4. Case 1. *A*, end result after second stage. *B*, end result; voiding.

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CONDYLOMATA ACUMINATA OF THE URETHRA*

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We have been impressed by the fact that little work has been done on the subject of condylomata acuminata involving the urethra. Only a few authors have mentioned the lesion when listing various pathologic processes that affect the urethra, and fewer still have written on the subject. No real study of the condition with its clinical and pathologic correlations has been made. For this reason our interest in the subject has been stimulated. Accordingly, we have made a clinical and pathologic study of all such cases encountered at the Mayo Clinic. The results of this study, together with a review of the literature, form the basis for this paper. Special attention will be given to the clinical picture, the histopathology, and the prognosis.

REVIEW OF THE LITERATURE

Etiology. Many years ago Kaposi mentioned that "condylomata acuminata owe their origin to the specific irritation of the skin by the gonorrheal discharge flowing over it." Most authors of the time agreed with him, and for many years syphilis was thought to play some part in the etiology of these lesions. However, as early as 1838 Ricord stated that careful clinical observations would serve to differentiate syphilitic condylomata from those of the acuminata type.

Frey found that two thirds of his patients with condylomata acuminata were free from syphilis, gonorrhea, or other disease of the genito-urinary tract, and that 50 per cent had, or gave a history of, common warts.

Verruca vulgaris, verruca digitata, verruca filiformis, verruca plantaris, verruca juvenilis, and verruca (condyloma) acuminata are the six varieties of warts found in man which are believed to be auto-inoculable and contagious. The causative micro-organism has not been definitely identified but it is considered by most authorities to be a filtrable virus.

As early as 1895 Judassohn demonstrated the contagiousness and transmissibility of warts by successful inoculation experiments. Since that time several authors (Kingery; Serra; Wile and Kingery) have duplicated his work.

Two factors, or contributing factors, having specific reference to etiology in women are chronic vaginal discharge and pregnancy. Almost all authors agree that condylomata acuminata are more frequently seen in women with chronic, profuse, vaginal discharge; Counseller and co-workers call attention to this factor in two articles. Dover, Phaneuf, Wilson, Benschine, Footer, and others point out that condylomata acuminata grow rapidly during pregnancy. In some cases large lesions which developed during pregnancy have completely disappeared, without therapy, after delivery. These men say that increased hyperemia of the

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variety of opinions as to the treatment of condylomata acuminata. The recommended treatment varies from that based on ideas of spontaneous disappearance to electrocoagulation, radium therapy, and the application of podophyllin.

Since Kaplan's original work with podophyllin in the treatment of condylomata acuminata many authors (Cohen; Culp and Kaplan; King and Sullivan; MacGregor; Reich, Nechtow and Rubenstein; Sullivan and King) have duplicated his findings. All authorities indicate that podophyllin is extremely effective and almost specific in the treatment of this condition.

Podophyllin is described by Cook and La Wall as an amorphous powder varying in color from light brown to greenish yellow, turning darker brown when exposed to heat or light. They speak of it as having a bitter taste, being irritating to mucous membranes, and forming the base for many proprietary "liver pills." Wood and Osol describe its active principle as a resin of the mandrake or May apple.

Biberstein has done some interesting work with vaccine therapy and says that this form of treatment is indicated at times when other methods have failed or are not practical. Wolters and Hesseltine have advocated radium therapy for these lesions.

PRESENT STUDY AND COMMENT

The cases for this study were obtained by reviewing the records of all urethral lesions seen at the Mayo Clinic in which it was felt a diagnosis of condylomata acuminata could possibly be made. To accomplish this, both the history and pathology files were used. Cases studied included those in which the following types of diagnosis had been made: condylomata acuminata, inflammatory lesions in general, papillomas, epithelial hyperplasia, carcinoma in situ, and all low-grade (grades 1 and 2) papillary epitheliomas. In all, 61 cases were selected for the study and multiple sections of each specimen were made for microscopic examination. Of this group, 27 proved to be cases of condylomata acuminata. The case records of this group of 27 patients were carefully studied and follow-up letters were sent to each patient.

Etiology. It was not within the scope of this study to place particular emphasis on the etiologic phases of condylomata acuminata. However, special attention was given to associated diseases of the genito-urinary tract: chronic vaginal discharge in women, chronic prostatitis and stricture in men, gonorrhea and syphilis were the associated diseases we felt worthy of special note. Although some of these diseases were noted along with condylomata acuminata of the urethra, we were unable to correlate any of these or other diseases as definite etiologic factors in this condition.

Although condylomata acuminata of the urethra may be associated with similar lesions on the genitalia, this is not necessarily the case. In 78 per cent of the cases studied there were no other demonstrable lesions on the genitalia. In not a single case were there warts elsewhere on the body.

Condylomata acuminata involving the urethra do not appear to present any special etiologic problems or throw any light on the subject in general. We agree parts, plus some hormonal factor, is probably the explanation for this peculiar action of these lesions during pregnancy.

Incidence and clinical picture. Authors agree that condylomata acuminata may be seen in any age group but are much more common between the ages of 15 and 40 years. It is understandable that men working with different age groups quote varying figures as to the over-all incidence. Authors (Creadick; Rulison; Wolters and Hesseltine) quoting figures from civilian hospitals and outpatient clinics indicate that the lesion is quite rare, whereas authors (Culp and Kaplan; Gersh) quoting statistics gathered in the Army during World War II indicate that such lesions are rather common. All agree that urethral involvement is relatively rare.

Culp and Kaplan in 1944 reported 200 cases of condylomata involving the genitalia in soldiers; of this group 10 patients presented urethral lesions. Under similar circumstances Gersh reported on 130 patients, 7 of whom presented lesions within the urethra.

Goldenberg in 1891 reported a case of condylomata acuminata involving the urethra in a 24-year-old man. The presenting symptom in this case was a chronic urethral discharge. Since that time several authors (Jacobsen and Jones; Jacobsohn; Kingery; Lazarus; Morrow; Palmer; Reich, Nechtow and Rubenstein) have reported practically every symptom referable to the urethra as being seen in such a group of patients. The chief symptoms reported were discharge, frequency of urination, dysuria, hematuria and urethral bleeding, difficulty in voiding or a forked stream, dribbling, and a urethral mass which was either palpable or which presented at the meatus.

Histopathology. Ash and Friedman give a very clear-cut and concise description of this lesion. They mention the deep fissuring of the acanthotic, hyperkeratotic or parakeratotic surface layer and state that this is responsible for the characteristic cauliflower appearance. These authors say that multiple branching of the stalked processes and the large amount of epithelial tissue, in proportion to the scarcity of the poorly vascularized connective tissue, distinguish condylomata from true fibro-epithelial papilloma.

Reich, Nechtow, and Rubenstein call attention to the chronic inflammatory reaction of the stroma and state that lymphocytic and plasma-cell infiltration is always present.

Ormsby and Montgomery point out that many mitotic figures are seen in these lesions and that the high degree of acanthosis often results in the erroneous diagnosis of epithelioma.

Loewenstein gives a very interesting discussion in writing on carcinoma-like condylomata acuminata. In this group of lesions the microscopic picture is exactly the same as that of other condylomata acuminata, but the former have a tendency to spread along the surface and even to penetrate the deeper tissues. Loewenstein says that this is not an active infiltration but is simply due to displaced condyloma tissue. He states that there is never any involvement of vessels, or metastasis.

Treatment. In reviewing the literature one is quite fascinated by the wide near the meatus, the symptoms usually were confined to urethral bleeding or the patient noted the growth. In those cases in which the lesions were more removed from the meatus the other symptoms mentioned were more pronounced. As one would expect, the more extensive the growth, the more severe the symptoms.

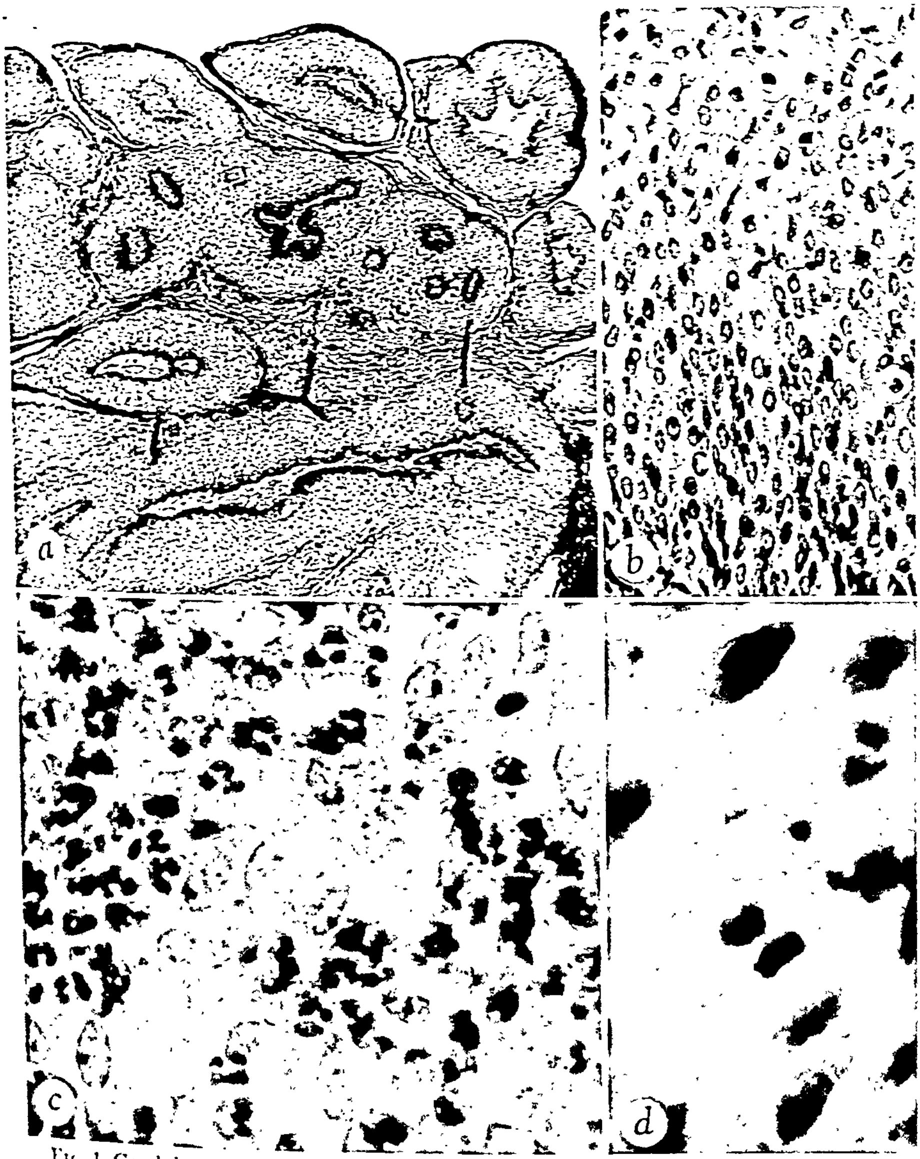

Fig. 1. Condylomata acuminata. *a*, General pattern of epithelium and its relationship to stalk (hematoxylin and eosin X 250). *b*, Cellular detail from stalk to surface (bottom to top) (hematoxylin and eosin X250). *c*, Infiltration by polymorphonuclear leukocytes (hematoxylin and eosin X825). *d*, Typical mitotic figure in the center of field (hematoxylin and eosin X 1,000).

with the literature that the infectious nature of warts seems to have been proved and that the etiologic agent is probably a virus. As is stated in the literature a definite history of contact is difficult or impossible to ascertain.

Incidence, sex and age distribution. The relative rarity of this lesion is clear from the few cases cited in the literature and the small number of cases in this series. In our group the lesions were fairly evenly distributed as to sex, although the male urethra was involved slightly more often. The ages of the patients varied from 2 to 61 years with an average age of 40 years. Sixty-five per cent of the patients were under 50 years of age.

TABLE 1. *Symptoms in 27 cases of condylomata acuminata of the urethra*

SYMPTOMS	CASES	PER CENT
Burning, frequency and urgency	22	81
Hematuria and urethral bleeding	10	37
Growth noted in urethra	10	37
Urethral discharge	7	26
Change in character of stream	6	22
Fistula formation	1	4
Dyspareunia	1	4
None	1	4

TABLE 2. *Location of the lesion*

LOCATION	CASES	PER CENT
Just inside meatus	13	48
2–2.9 cm. from meatus	8	30
3–3.9 cm. from meatus	3	11
Entire urethra involved	3	11
Prostatic and membranous urethra alone	0	0
Total	27	100

Clinical picture. When condylomata acuminata involve the urethra, no symptom or group of symptoms seems to be specific. As one would expect, almost any symptom referable to the urethra was noted in this group of patients.

The most common symptoms noted were those due to urethral irritation, namely, frequency, burning, and urgency of urination. Such symptoms were noted in 81 per cent of the cases. In 37 per cent hematuria and urethral bleeding were the presenting symptoms, and in the same percentage of cases the patients noted the growth presenting at the meatus or felt the lesion along the urethra. Urethral discharge and some change in the character of the urinary stream were other symptoms frequently noted (table 1).

The duration of symptoms was quite variable. One patient gave a history of symptoms for 15 years, but the average duration was 6 to 12 months. There seemed to be no specific group of symptoms referable to the sex involved.

The location, size, and number of the lesions apparently have a definite relationship to the clinical picture. When the lesions were limited to the urethra

The only reported complication resulting from treatment was that of a man in whom a urethral stricture developed following radium therapy that had been administered elsewhere (table 3).

At this point it would seem appropriate to point out that practically all authors (Clark) writing on carcinoma of the urethra state that these lesions present a much better prognosis when the anterior portion of the urethra is involved than when the lesion is located in the posterior portion. Since condylomata acuminata primarily involve the anterior portion and at times are difficult to differentiate from carcinoma, one has to speculate that possibly some of these cases of carcinoma include cases of condylomata acuminata. This would account, at least in part, for the marked difference in prognosis between lesions involving the anterior and posterior portions of the urethra.

Treatment. It is not within the scope of this paper to make a critical and detailed evaluation of the various methods of treatment. However, we should like to draw a few general conclusions which we feel are essential in the proper care of patients with condylomata acuminata.

TABLE 3. *Follow-up and survival studies*

	CASES	PER CENT
Total	27	
Condition followed	23	
Condition followed 5 years or more	21	
Recurrence	1	4
Complications from treatment	1	4
Five-year survival	21	100

We feel that it is imperative to evaluate the condition of the entire urethra carefully by means of a urethroscopic examination when any part of it is suspected of being involved with condylomata acuminata or any other type of lesion. The exact location of the lesion or lesions should be noted along with any evidence of fixation or infiltration. If the lesion is limited to the posterior portion of the urethra alone, one should immediately suspect carcinoma. As noted previously, in this series not a single patient showed involvement of the posterior portion of the urethra alone. Of course, any gross evidence of infiltration would speak for carcinoma.

After careful inspection of the urethra adequate tissue should be removed for microscopic examination. If the characteristic features, as pointed out in the histopathologic description, are kept in mind, one should not confuse this lesion with carcinoma or other urethral lesions.

Once a diagnosis of condylomata acuminata has been definitely established any convenient and easily applicable method that will completely destroy the lesion should be acceptable. In this series all but 2 patients were treated by fulguration with the electrosurgical unit. In 2 cases in which there was extensive involvement of the entire urethra, radium therapy was employed with apparently good results.

Podophyllin therapy seems to be almost specific for condylomata acuminata and is probably the treatment of choice. It would seem that in lesions involving

One of the most striking, and we believe one of the most significant features of this study, is the fact that the anterior portion of the urethra was involved in 100 per cent of the cases. In 3 cases, or 11 per cent, the entire urethra from the meatus to the vesical neck was involved. In no case was the posterior portion of the urethra involved alone (table 2).

Histopathology. As has been previously mentioned, 61 suspicious lesions of the urethra were studied. Of this number, 27 were condylomata acuminata. In all microscopic sections special attention was given to the character and pattern of the surface epithelium and its underlying stroma or stalk. A careful study relative to cellular detail and mitosis was also made. Whether the lesions had a tendency to infiltrate was also noted.

In general these lesions are characterized by large, irregular infoldings or fissuring of the thickened surface epithelium. The stalk is very small and scanty in comparison with the proliferative surface epithelium (fig. 1, *a*). The surface epithelium presents unusual keratinization. Just beneath the surface large clear cells may be seen. These are believed to be cells in which the keratin has been dissolved out by the fixing process. Although the epithelium is quite cellular, all cells are arranged in a very orderly manner (fig. 1, *b*). Mitotic figures are present and they, along with the other changes mentioned, are often the pitfalls in diagnosing these lesions erroneously as carcinoma (fig. 1, *d*). One of the most striking features noted in these sections was the marked leukocytic infiltration. The polymorphonuclear leukocytes were by far the most prominent infiltrating cells noted (fig. 1, *c*). In no case was there any tendency for the lesion to involve surrounding tissues or vessels.

In contrast to this lesion the papillary epitheliomas present small, frail, papillary projections of the surface epithelium. The stalk is rather prominent in its relation to the epithelium. Leukocytic infiltration is not noted. These lesions are malignant and do infiltrate vessels and the surrounding tissues.

It is felt that if the features just mentioned are kept in mind, one will not confuse this entirely benign lesion of the urethra with carcinoma.

Follow-up and survival studies. The follow-up study confirmed the clinical and histopathologic impression that these lesions of the urethra are entirely benign and present an excellent prognosis.

Although the total number of patients in this series was 27, only 23 were traced; 4 patients did not respond to repeated communications. Of the 23 traced patients, 2 had had their original examination within the previous 2 years, so that adequate time had elapsed to permit accurate evaluation of the condition of only 21 of these patients.

In the 21 cases in which the patient's condition was followed for at least 5 years, the survival rate was 100 per cent. The longest time a patient in this group was followed was 23 years.

We were rather surprised that the recurrences were not more prevalent. Only 1 of the 23 patients showed any recurrence. This patient, a man, noted recurrent lesions 6 or 8 weeks after treatment. In answering the inquiries 3 years later he stated that these lesions were still present but were not troubling him. His general health was good.

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the urethra which are extensive or are far removed from the meatus, the accurate application of this solution might present some problem.

Because of some tendency to recurrence (4 per cent in this series), the condition of all patients should be followed for a period of six to twelve months.

Whatever form of therapy is employed in these cases one important factor should be kept in mind: the lesion is benign and should not be overtreated; with destruction of too much tissue, fistula or stricture or both may result. It would seem advisable to treat the lesion several times rather than cause a fistula or stricture of the urethra.

The cardinal point to remember in handling these urethral lesions is to make an accurate diagnosis and then treat the condition conservatively. A radical operation should never be done for simple, uncomplicated condylomata acuminata of the urethra.

SUMMARY AND CONCLUSIONS

This paper is based on a complete review of the literature and a review of the records of 27 cases of condylomata acuminata of the urethra encountered at the Mayo Clinic, including follow-up of patients and study of microscopic sections of pathologic specimens.

No specific etiologic factor has been demonstrated. The contagious and infectious nature of the lesion seems to have been established and the causative organism is probably a filtrable virus. A history of contact is difficult or impossible to demonstrate in most cases.

These lesions are usually seen in the younger age groups. The average age in our series was 40 years. The chief symptoms noted were those of urethral irritation, namely, frequency, urgency, and burning on urination. Urethral discharge, hematuria, and urethral bleeding were other frequently noted symptoms.

The location of the lesion in the urethra is most important. In 100 per cent of the cases in our series the anterior portion was involved. In 11 per cent the entire urethra was affected, but in no case was the posterior portion involved alone. One should be very skeptical of the diagnosis of condylomata acuminata when only the posterior portion of the urethra is involved.

Adequate study of the urethra and microscopic sections of tissue removed are essential for an accurate diagnosis. Because of the cellular nature of this lesion and the presence of mitotic figures one must be ever alert to differentiate it from carcinoma.

Condylomata acuminata are definitely benign lesions and should be treated as such. Radical surgical treatment should never be given for a simple, uncomplicated lesion. Any form of therapy that will completely destroy the lesion is acceptable. Care should be taken not to produce a fistula or a stricture of the urethra. Because of some tendency to recurrence, the condition of these patients should be followed for 6 to 12 months.

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lymphogranulomatosis (Hodgkin's disease) and the disease they were studying. It was not until 1925 that Frei[2] by the introduction of a specific skin antigen paved the way for accurate identification of this disease. Proof that the disease was caused by a filterable agent transferable to monkeys by means of intracerebral inoculation was furnished by the Swedish group of Hellerstrom and Wassen in 1930. In 1940, Rake, McKee, and Shaffer[3] cultivated the viral like agent in the yolk sac of the embryonated chicken's egg. This resulted in the production of a concentrated suspension of elementary bodies, and by using these newer techniques, a highly purified specific antigenic agent was prepared, which is now used for a specific complement fixation test.

CLINICAL PICTURE AND DIAGNOSIS

The first clinical manifestation of lymphogranuloma venereum is a primary lesion appearing about 7 to 12 days[4] (up to 21 days) after infective exposure and usually located on the genitals although occasionally occurring extragenitally. This lesion which is transient and inconspicuous most often occurs as a small herpetiform vesicle or ulcer which in the male is seen on the shaft or glans of the penis near the coronal sulcus, while in the female it may appear on any part of the vulva, but is located most commonly in the region of the fourchette. It disappears in a few days without causing constitutional symptoms. Other primary types which may be seen include a syphiloid, nodular and infiltrated type as well as an occasional primary balanitis or urethritis. Primary lesions have been noted in from 3 to 53 per cent of cases in different clinical series.

The next stage in the usual evolution of the disease process in the male and the one which can be easily confused with incarcerated femoral hernia is the phase of acute inguinal lymphadenitis. This occurs 10 to 30 days after the initial exposure but occasionally may be prolonged up to 50 days or more. It is this inguinal adenopathy and associated pain which often first calls attention to the disease. Adenopathy was unilateral in about 40 per cent of one series of cases[5] but in other groups has been unilateral in up to 70 or 80 per cent. These nodes, which are at first discrete and freely movable under the surface of the skin, rapidly tend to become adherent and coalesce. This results in an inflammatory mass over which the skin may take on a dusky red tint and subsequently undergo suppuration and sinus formation. A few glands, however, apparently swell and regress spontaneously without suppuration. Healing is usually accompanied by scarring at the site of the bubo. Pathologically[6] the lymph nodes reveal acute and chronic inflammation with small discrete areas of necrosis surrounded by densely packed endothelial cells. The purulent discharge from such a bubo was the source of the original Frei antigen. This type of inguinal infection although commonly seen in men is rare in women due to the fact that the primary lesion in the female is usually located intravaginally and therefore the infection, carried by lymphatic

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[2] Frei, W.: Klin Wchnschr., 4: 2148, 1925. Prior translation.

[3] Rake, G., McKee, C. M. and Shaffer, M. F.: Proc. Soc. Exper. Biol. & Med., 43: 332, 1940.

[4] Greenblatt, R. B.: Venereal Disease Information, Supplement No. 10.

[5] Costello, M. J. and D'Avanzo, C. S.: Arch. Dermat. & Syphilology, 57: 112, 1948.

[6] Karsner: Human Pathology. Philadelphia: Lippincott, 1942.

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ACUTE LYMPHOGRANULOMA VENEREUM: A SHORT REVIEW WITH OBSERVATIONS ON THE SURGICAL IMPLICATIONS AND CHANGING GEOGRAPHIC DISTRIBUTION

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Lymphogranuloma venereum is a widespread communicable disease almost always acquired through venereal contact and caused by a specific filterable agent which falls into the psittacosis group of infectious agents. Synonyms which have confused the accurate identification of this disease include lymphopathia venereum, climatic bubo, venereal bubo, tropical bubo, strumous or scrofulous bubo, poradenitis, venereal lymphogranuloma, esthiomene, nontuberculous granulomatous lymphadenitis, lupus vulvai, fourth venereal disease, sixth venereal disease, Nicolas-Favre disease, malady of Durand, and others. Confusion with two other diseases, granuloma inguinale and lymphogranulomatosis (Hodgkin's disease) is an error which is too often made.

In the United States the occurrence of this disease has been in the past largely confined to the Southern Negro; however with the mass movement of population groups brought about by military service and war industry there is every indication that the condition is becoming more common in areas where it has rarely been encountered before. Early diagnosis of this disease by the Frei intradermal test and/or the complement fixation test has assumed a new importance because of the therapeutic effect of aureomycin and other new antibiotic drugs.

Interest in lymphogranuloma venereum by the surgical service at this hospital has been recently stimulated by 2 cases of inguinal bubo having been admitted to the hospital with a mistaken diagnosis of incarcerated femoral hernia. The purpose of this paper is to present these 2 cases and two other cases of chronic lymphogranuloma under observation in the last year.

A brief review of this disease will be given including its differential diagnosis from incarcerated femoral hernia and newer concepts of therapy.

An analysis of the reported incidence of this disease in the Wichita-Sedgwick County area and the State of Kansas is also included together with its implications.

HISTORY

Infectious buboes apparently unaffected by conventional antiluetic therapy have been described by numerous investigators back as far as 1786. In 1913, Durand, Nicolas, and Favre[1] published their results of a long period of study on a group of cases of this disease which they unfortunately termed "lymphogranuloma inguinale" because of the similarity between the histologic picture of

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[1] Durand, M., Nicholas, J. and Favre, M.: Bull. et mem Soc. med. d. hop. de Paris, **35:** 274, 1913. Prior translation.

Past history and system review were noncontributory. Physical examination on admission to the surgical service revealed a well nourished, ambulatory man who apparently had an upper respiratory infection. Both ear drums were slightly reddened, tonsils were enlarged, lobulated, and injected. Examination of the chest and heart were within normal limits. Examination of both inguinal areas revealed small external rings without impulse on coughing. In the left inguinal area, there was a subcutaneous mass somewhat flattened about 3 by 2 by 1 cm. in size which was slightly movable. It lay lateral to the external ring directly over Poupart's ligament, and had a solid rather than cystic feel. No lymph nodes were palpable in any other areas of the body. The initial impression of the examining physician was that the patient had an upper respiratory infection with inguinal lymphadenopathy on the left, possibly due to trauma, although a femoral hernia containing omentum could not be positively ruled out. Temperature on the day of admission was 101.2F, pulse 100 and respirations 18. Initial laboratory work revealed a negative serology, essentially normal urine, and a white count of 11,250 with 61 polys, 23 lymphocytes, 14 monocytes, and 2 eosinophils. Red blood count was 4,670,000. The sedimentation rate was 21 millimeters per hour.

The patient was observed for a few hours and seemed to show no evidence of intestinal obstruction or of acute intra-abdominal disease. The history was carefully reviewed and the information then elicited that the patient had been in Cuba approximately 5 weeks before, at which time he had had intercourse with a native. No condom was used although a prophylactic kit was employed following intercourse. No penile lesion had been noted at any time. With this new information available, a tentative diagnosis of lymphogranuloma venereum was made and the patient placed on crysticillin 300,000 units twice daily and chloromycetin 250 milligrams every 4 hours. A Frei skin test was made and was a borderline positive. The heterophil antibody test was negative. Complement fixation tests for lymphogranuloma venereum were 4 plus in all dilutions through 1 to 40, 1 plus in a dilution of 1 to 80, and negative in a dilution of 1 to 160. Subsequent complement fixation tests revealed the same results. Total proteins were 8.7 with an albumin-globulin ratio of 5.9 to 2.8. On July 26 chloromycetin was discontinued and aureomycin 250 mg. 4 times daily was started and carried through July 30. On August 3, crysticillin was discontinued, and since the adenopathy in the left groin had regressed and appeared stationary as a small nodular area, it was felt that the patient had achieved quiescence of his disease. He was therefore discharged on August 6, 1950.

He was re-admitted to the hospital August 21, because of a recurrence of tender, swollen lymph nodes in the left inguinal area. Interval history revealed that he had been well until August 17, four days prior to re-admission at which time tenderness in the left inguinal area recurred. Physical examination was essentially as on the previous admission except for the left inguinal area which on this occasion showed a group of enlarged tender nodes. Generalized lymphadenopathy including axillary and epitrochlear nodes was also noted. The largest of the lymph nodes in the left inguinal area was 1½ cm. in diameter. Serology was again negative as was the urinalysis. White count was 11,250 with an essentially drainage, spreads posteriorly to intrapelvic glands where manifestations of the disease first become evident. For the description of the anorectal type of infection with proctitis or proctitis and stricture formation, the reader is referred to more detailed works.[4, 7, 8, 9, 10, 11, 12]

Suffice it to say here that the disease tends to become chronic and may be seen in this form on the genitals, in the pelvis, in the rectum, in the joints, in the urethra, in the bladder, in the eye, in the brain, in the pleural cavity and elsewhere. Lymphogranuloma venereum in the acute early inguinal stage is usually associated with headache, fever up to 104F, weakness and malaise. Anemia and hyperproteinemia[13] may be noted. The Frei intradermal test, which is considered diagnostic, is a simple skin test which may be carried out with either the original Frei antigen or the newer yolk sac preparations. A positive test (a papule of 7 mm. or greater in diameter at the end of 48 to 72 hours) signifies either present or past infection with the agent of lymphogranuloma venereum and is 95–100% accurate.[14] This test becomes positive 7 to 40 days after the appearance of inguinal adenitis and should be repeated if found negative early in suspected cases. Complement fixation tests are readily available with yolk sac suspension antigen (lygranum antigen), and the correlation of findings from these tests with findings from the intradermal tests are high.[15] Although more difficult to perform, the complement fixation tests are probably of more value since they do give some clinical indication as to the activity of the disease. It has been shown that a 4-plus reaction in dilutions of 1 to 5 is of positive diagnostic significance for previous infection, while 4-plus agglutination in titers of 1–20 or 3-plus in titers of 1–40 suggests recent or acute disease.[16] Complement fixation may be encountered in initial dilutions of serum as high as 1 to 320 and occasionally higher.

CASE REPORTS

Case 1. H. R., a 23 year old white male aircraft worker, was admitted to the hospital on July 22, 1950, with the chief complaint of a tender mass in the left inguinal area. He had attributed this soreness to trauma from leaning against a rail while at work. Two days before admission, he had a sensation of fullness in the left inguinal area associated with chills and fever. A small lump was felt the next morning and the day after that a definite lump was present in the left inguinal area which was tender and painful on walking. He consulted a physician who told him that he had an incarcerated femoral hernia which would require immediate operation and he therefore presented himself at the hospital for surgery.

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[7] van Rooyen and Rhodes: Virus Diseases of Man, Nelson, 1948.

[8] Meyer, K. F.: From Viral and Rickettsial Infections of Man, T. M. Rivers. Philadelphia: Lippincott, 1948.

[9] Cecil: Textbook of Medicine. Philadelphia: Saunders, 1943.

[10] Manson's Tropical Disease. Baltimore: Williams & Wilkins, 1945, 12 ed.

[11] D'Aunoy, Rigney and von Haam, E.: Arch. Path., 27: 1033, 1939.

[12] Stitt: Diagnosis, Prevention and Treatment of Tropical Diseases, Strong, Seventh Edition, 1944.

[13] Howard, M. E., Eisenman, A. J. and Strauss, M. J.: Am. J. Syph., Gonorr. & Venereal Dis., 23: 83, 1939.

[14] Grace, A. W.: Venereal Disease Information: 22: 349, 1941.

[15] Axelrod, S. J.: Am. J. Syph., Gonorrhea, and Venereal Dis., 26: 474, 1942.

[16] Luger, N. M.: Am. J. Syphilis, Gonorrhea and Venereal Dis., 34: 351, 1950.

showed an occasional white blood cell but was otherwise normal. Serology wa negative. Heterophil antibody test was negative on two occasions.

The patient's temperature ranged from 100 to 102F for the first week afte which time he became afebrile and remained so for the subsequent period o hospitalization. Frei test was equivocal on March 19, but was strongly positiv on April 2. The patient was treated with aureomycin 250 mg. q.i.d.; crysticilli 300,000 units b.i.d.; and sulfadiazine gm. 1 q.i.d. for a period of 6 weeks. Th nodes decreased slightly in size and tenderness under this therapeutic regime with the exception of one large node in the left inguinal area. Because of the per sistence of this node, a left inguinal gland dissection was done on April 10, 1951 and all of the nodes removed en bloc. Postoperative course was satisfactory although the wound had to be aspirated on two occasions because of small col lections of serum. The generalized adenopathy gradually diminished. Pathologi report on the excised lymphatic nodes revealed chronic lymphadenitis with foca necrosis of lymph nodes consistent with lymphogranuloma venereum. At th conclusion of his 6 weeks of aureomycin and sulfadiazine therapy, the patien was asymptomatic and had only a few residual small shotty nodes in the lef inguinal area. The site of excision was soft and nontender and the operativ wound was well healed. The patient was therefore discharged on May 5, 1951 with the recommendation that he return for re-evaluation in one month.

Case 3. A third case of far advanced lymphogranuloma venereum with mul tiple perineal sinuses and a rectal stricture was also treated on the surgical serv ice at the VA Hospital, Wichita, Kansas, from July 5, 1950, to July 16, 195 He was a Negro and his Frei test was strongly positive for lymphogranulom venereum. Complement fixation studies were not done.

Case 4. A fourth patient with lymphogranuloma venereum is in the hospit at the present time and is being treated for a progressive stenosing urethriti He is also a Negro and both his Frei test and complement fixation tests are pos tive; the latter in a dilution of 1 to 5.

DISCUSSION

In regard to the first 2 cases presented here, it is interesting to note that neith gave a history of a primary lesion. The Frei test was negative or equivocal i both cases on admission to the hospital but subsequent testing showed a defini positive reaction. Both cases were believed to have complicating upper respir tory infections upon admission to the hospital because of malaise, fever, rhiniti etc. In regard to the differential diagnosis between an incarcerated femoral he nia, particularly an incarcerated femoral omentocele, and a solitary lymph no in the area of the femoral ring, physical findings help but little. Bailey[17] stat that, if no obvious cause for regional lymphadenopathy is present, such as a infective focus on the feet, legs, anorectal, genital, or perineal areas, there a no physical signs which will elucidate the difference. Bilateral lymphadenopat normal differential. The Frei skin test was repeated and was clearly positive (8 mm). Heterophil antibody test on this occasion remained negative. On August 23, the patient was taken to surgery where, under local anesthesia, one of the left inguinal lymph nodes was biopsied. Microscopic examination revealed chronic inflammation of the lymph node, nonspecific in character. Complement fixation tests were obtained from the Communicable Disease Center of the United States Public Health Service, Chamblee, Georgia, and were positive in a dilution of 1 to 128 with Lygranum antigen. The patient was again started on aureomycin on August 25 receiving 250 mg. 4 times a day for 5 weeks, as well as sulfadiazine 1 gm. 4 times a day, for the same period. Under this regimen the nodes and induration rapidly disappeared from the left inguinal area and the patient became asymptomatic. He was discharged well on September 29, 1950.

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[17] Bailey: Physical Signs in Clinical Surgery. Baltimore: Williams & Wilkins, 1946.

Case 2. Mr. D. G. was first seen at the hospital on March 17, 1951, in the admitting department and was sent to the surgical service with a tentative diagnosis of incarcerated femoral hernia. He was a 26 year old Negro, married porter whose chief complaint on admission was a painful lump in the groin first appearing on March 7 about 10 days prior to admission. No tenderness was noted at that time although the lump continued to enlarge during the following week. On March 15, two days prior to admission, it became painful and markedly tender to touch. There was no associated nausea, vomiting, change in bowel habits, urinary difficulty, or other symptoms except for mild rhinitis. The patient had had one previous episode of swollen glands in 1944, several weeks following an episode of gonorrhea. At that time a Frei antigen test was apparently negative. He also gave the history of extramarital sexual contact 3 weeks prior to admission. No contraceptive agent or prophylaxis was used. No history of a penile lesion was given nor any evidence of dysuria or urethral discharge.

Past history was essentially negative except for recurrent sinusitis. System review was entirely negative except for the complaints noted in the present illness. Physical examination on admission revealed a well developed, well nourished Negro who appeared acutely ill. Temperature was 102F, blood pressure 112/86. Head and neck were essentially negative, as were the heart and lungs. There was a small umbilical hernia present. No abdominal tenderness was noted although the entire left groin was tender. No inguinal hernias were present. An enlarged, markedly tender mass measuring approximately 2½ cm. in diameter presented in the left groin. It was freely movable, gave no pulsation on coughing or straining, and was located just inferior to Poupart's ligament. It was surrounded by multiple shotty hard lymph nodes both above and below the ligament. Multiple hard, nontender nodes were also noted in the right inguinal area, and in addition to the inguinal adenopathy bilateral axillary and cervical adenopathy was present. No epitrochlear nodes were palpated. The initial impression was probable lymphogranuloma venereum. X-rays of the chest and abdomen on admission to the hospital were within normal limits. Original laboratory work revealed a blood count of 12,000 with 70 polys, including 12 stabs, 19 lymphocytes, 10 monocytes, and 1 eosinophil. Red count was 5,060,000. Urinalysis studies suggested that in spite of apparently good clinical results, therapy with sulfonamides may well be producing latent disease rather than cure; and because of the devastating late effects of lymphogranuloma venereum which has gone through a clinically latent period, a virucidal drug was still sought. Wright[19] in 1948 stated that prior to the clinical use of aureomycin in the treatment of lymphogranuloma venereum an effective treatment was not yet available for this disease. It was his impression after 24 years of experience with the therapy of this disease that antimony potassium tartrate, stibophen (fuadin), penicillin and even sulfa controlled only the secondary infection leaving the basic disease process due to the viral agent untouched. With the introduction of aureomycin, however, and its subsequent application to the treatment of lymphogranuloma venereum, the answer may have been found. Different workers[20,21] have shown that following aureomycin therapy, lymph nodes proved by aspiration to contain active agents before therapy no longer showed the presence of these agents on subsequent aspirations following therapy. There has been poor correlation, however,[20,22] between the clinical results obtained, and follow up complement fixation serial studies. Much work remains to be done to clarify this picture. Although final proof of the virucidal properties of aureomycin must remain for more adequate studies, it most assuredly has a strong antiviral effect and appears to be the drug of choice in the treatment of this disease. Recommended dosages are 250 mg. orally, 3 or 4 times a day for a period of 2 to 6 weeks. This should be given while the patient is at bed rest since bed rest has been shown by all reporting groups to be highly valuable.

Whether or not chlormycetin, terramycin or other new antibiotic agents will play a part in the treatment of this disease must remain for future controlled clinical experiments to show.

With regard to the surgical approach to the acute inguinal form of lymphogranuloma venereum, there has been a good deal of debate. Aspiration of fluctuating lymph nodes[5,22] as well as incision and drainage or even extirpation of involved glands have all been long used and are still advocated by some workers.[11] Opponents of this school of thought, however, believe that aspiration, or incision and drainage pave the way to chronic fistula formation; and that extirpation may be a prominent factor in the future development of postoperative elephantiasis of the genitals because of further disruption of normal lymphatic drainage. With the advent of modern aureomycin therapy, however, it is improbable that aspiration of fluctuant buboes, especially if done through an area of normal skin, will lead to the production of sinuses. Aureomycin therapy has already paved the way for a more radical surgical approach to severe rectal strictures in regard to resection and short circuiting procedures and will doubtless pave the way for a more radical surgical extirpation of involved inguinal nodes. D'aunoy and von Haam,[23] in their excellent monograph on the subject of lymphogranuloma vene-

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[19] Wright, L. T., Sanders, M., Logan, M. A., Prigot, A. and Hill, L. M.: J. A. M. A. 138: 408, 1948.

[20] Runyan, et al.: Am. J. Med., 9: 419, 1949.

[21] Alergant, C. D.: Lancet, 1: 930, 1950.

[22] Laube, P. J.: Chinese Med. J., 67: 137, 1949. Prior translation.

or generalized lymphadenopathy, of course, suggests the lymphatic origin of confusing masses.

In regard to the diagnosis of lymphogranuloma venereum as a cause of isolated inguinal or femoral adenopathy, complement fixation studies or skin testing with the Frei antigen, and most important, a detailed history with regard to possible infectious sexual contact will usually point the way toward the correct diagnosis. The constitutional symptoms seen in both our cases and most always found in early cases of acute inguinal lymphogranuloma venereum would seldom be found early in the course of a strangulated femoral omentocele, and usually would not be found without other manifestations of acute abdominal disease, such as vomiting, peritoneal irritation, etc. The differential diagnosis between solitary lymphatic tumors in the inguinal or femoral area and incarcerated femoral hernia containing bowel is usually much easier to make because of the gross manifestations of acute intra-abdominal disease which the latter would show. The finding of bowel sounds on auscultation or enclosed gas pockets on x-ray over an inguinal mass would also be pathognomonic of the latter condition. If, however, in spite of a careful history, physical examination, and x-ray studies, the differential diagnosis cannot be resolved, it must be emphasized that surgical intervention should follow without delay. Incision into, or dissection around, a lymphogranulomatous node or any other lymph node regardless of the pathologic process involved is certainly preferable to the neglect of an incarcerated or strangulated femoral hernia.

TREATMENT

Therapy employed in the past for acute inguinal lymphogranuloma venereum can be classified as chemotherapeutic, radiologic, hormonal, antigenic, antibiotic and surgical. In regard to chemotherapeutic agents many have been tried in past years with varying degrees of effect. Antimony preparations have been the most widely used including antimony and potassium tartrate, and various other commercial preparations. Iodides, copper salts, gold salts, glycerine and sodium salicylate were all used and shown to be relatively ineffective. Radiation with x-ray or radium proved to be of little value as did hormone therapy, antigenic therapy with the Frei antigen, diathermy and solid carbon dioxide.

Following the introduction of sulfa drugs, they were used alone or in combination with other agents extensively in the treatment of acute inguinal lymphogranuloma venereum. Sulfathiazole and other related sulfa drugs were of obvious clinical value in promoting reduction in the size of buboes, drying up of fistulous tracts, etc.[5] It was soon pointed out, however,[18] that sulfathiazole, although active in vitro, was virucidal only when employed in extremely high concentrations, concentrations much too high for clinical usage. It was also shown[19] that no laboratory animals "cured" with sulfa remained free from symptoms of the disease, but after many months developed signs of chronic hydrocephalus and, when sacrificed, yielded strains of the agent from the brain and other tissues. These

[18] Jones, H., Rake, G. and Stearns, B.: J. Infect. Dis., 76: 55, 1945.
[19] Jones, H., Rake, G. and McKee, C. M.: Proc. Soc. Exper. Biol. & Med., 48: 318, 1941.

colored population of the United States; more specifically that part of the colored population which is on a low educational, financial and social stratum.

Since lymphogranuloma venereum is a reportable disease in only four states the nationally reported statistics[28] are, not surprisingly, low. The reported incidence of this disease nationally in 1950, known military cases excluded, was only 0.1 case per 100,000 population in the white group and 9.4 cases per 100,000 in the non-white group giving a rate for all races of 1.1 cases per 100,000. (Compare to our incidence of 250 cases per 100,000 or the area incidence of 8 cases per 49,367 or 16 cases per 100,000.) The rate for non-white males is remarkably higher than all other figures being 14.3 cases per 100,000 general population.

In 1950, only 1 patient with lymphogranuloma venereum residing in the state of Kansas was reported to the State Board of Health[29] compared to a discovered incidence of all cases reviewed in this area of 16 per 100,000 (see last column of table 1). In the first part of 1951, two cases have been reported. Both of these were Negroes and were reported from the Venereal Disease Control Clinic in Wichita which during the statistical period of one year saw 805 patients, an incidence from this reporting clinic of 248 cases per 100,000 (compared to our incidence of 250 cases per 100,000). Since there is a large Negro population in the Sedgwick County-Wichita area (about 10 per cent of 245,000 total population) it is apparent that the reported incidence of cases of lymphogranuloma venereum diagnosed during hospital admissions in this area is far below that which might be anticipated from a comparison with similar population groups elsewhere. This suggests the presence of a large group of unrecognized cases of lymphogranuloma venereum, many latent, but a considerable number active and infectious in the Sedgwick County-Wichita and Kansas areas and other areas with a new influx of colored population. Because of the devastating late effects of this disease and because of the possibility of complete early cure by newer therapeutic methods a plea is made for the more frequent use of skin

TABLE 1. *Incidence of lymphogranuloma venereum diagnosed in the Wichita-Sedgwick County Area June 1950 to June 1951*

REPORTING AGENCY	TOTAL ADMISSIONS	CASES OF LYMPHOGRANULOMA VENEREUM	CASES PER 100,000
Hospital A	14,000	0	0
Hospital B	4,000	0	0
Hospital C	4,805	0	0
Hospital D	18,815	2	10.6
Hospital E (Charity Institution)	2,342	0	0
Surgical Service, VA Hospital, Wichita	1,600	4	250
County V. D. Control Clinic	805	2	248
Total	49,367	8	16.0

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[28] Statistical Letter, FSA-PHS-Div. of V.D., Office of Statistics, Nov., 1950.

[29] Kansas State Board of Health, Division of Venereal Disease Control, Robert H. Riedel, M.D., Acting Director, Personal Communication.

reum, point out that only local lesions such as the inguinal buboes are observed in a majority of patients because of rapid destruction of the etiologic agent within the human body. They therefore believe that removal of local lesions would remove the main source of possible further spread of the infection and thus be an extremely sound method of treatment. These workers used a surgical approach in the treatment of 85 patients with rather far-advanced glandular involvement and found that lymphadenectomy resulted in a markedly increased rate of healing; and that even incision and drainage caused healing to occur in a shorter period than that required for the abortive type (nonsuppurative lymphadenopathy). Eight months following conclusion of this series, none of the patients surgically treated presented edema or elephantiasis of the genitals.

In regard to the treatment of more chronic forms of lymphogranuloma venereum, particularly proctitis with rectal strictures, the reader is referred to more detailed papers.[24, 25] As previously mentioned, aureomycin will probably play a large part in the control of the infectious agent as well as secondary contaminants before, during, and after surgical procedures, which will allow a more radical approach to short circuiting and resection operations. It should be remembered, however, that no chemotherapeutic or antibiotic agent can ever change thickened, scarified, fibrotic tissue such as is found in chronic lymphogranuloma venereum back to normally functioning tissue. Early incomplete strictures of the rectum show a definite symptomatic improvement when placed on aureomycin,[20, 26] and this clinical response along with long and short wave diathermy and gentle rectal dilatations may allow more radical surgery to be postoponed or put off entirely.

INCIDENCE OF LYMPHOGRANULOMA VENEREUM IN THE WICHITA-SEDGWICK COUNTY AREA

When this paper was first outlined it was our intention to briefly compare our findings with those of other hospitals in the area. As information was collected, however, and in spite of the small total number of cases reported, it became quite apparent that there was a marked discrepancy between the incidence of disease in this area which might be anticipated and the number of cases diagnosed upon hospital admission. In the charity hospital of Louisiana, D'aunoy and von Haam[11] found an incidence of positive Frei tests in 17.4 per cent of all colored admissions. S. H. Gray and co-workers at St. Louis[27] on routine testing in the venereal disease center found positive reactions in about 40 per cent of Negroes and 3.4 per cent of white patients. Luger[16] testing Negroes employed in Petersburg, Virginia found 42 per cent positive complement fixation reactions. Further serologic data by him comparing a collegiate Negro group and the general white population of the same city disclosed a similar rate of active disease in these two groups which was less than 2 per cent in either case. These figures point strongly to the large reservoir of lymphogranuloma venereum in the

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[24] Navarro, A.: La prensa medica argentina, 36: 2567, 1949. Prior translation.

[25] Wright, L. T. Freeman, W. A. and Bolden, J. V.: Arch. Surg., 53: 499, 1946.

[26] Fletcher, A., Sigel, M. and Zintel, H. A.: Arch. Surg., 62: 239, 1951.

[27] Gray, S. H., Hunt, G. A., Wheeler, P. and Blache, J. O.: J. A. M. A., 106: 919, 1936.

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URINARY CALCULI AMONG NEGROES OF BELGIAN CONGO, AFRICA

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During a period of almost seven years of medical and surgical practice in the Belgian Congo, Africa we were struck with the rather frequent occurrence of urinary bladder calculi among the natives of our region. That this might be of significance did not occur to us until the reading of the article by Dodson and Clark in which it was pointed out that urinary calculi are practically unknown among the natives in Africa. They stated: "The Negro is generally believed to be particularly immune to this disease."

Examination of the literature on this subject to date supports the statement of Dodson and Clark.

In Hinman's *Principles and Practice of Urology* the statement is made: "The most notable stone districts (India, Mesopotamia and South China) lack proper sanitation and suitable food but the African Negro, similarly deficient, is almost immune to stone."

In writing on the etiology of stone J. Swift Joly made the statement: "On turning to the racial incidence of lithiasis, one is struck by the comparative immunity of the Negro."

Again Holmes and Coplan, in discussing the geographic incidence of urolithiasis, state: "We have called attention to what we believe to be a fact, that the Negro shows little tendency to stone formation, although the urines of those who work in the cotton fields of the South are habitually concentrated."

Vermooten came to the same conclusion as the aforementioned writers after he made a careful study of the problem in South Africa. At Dr. Vermooten's request, the examination of case records covering one million Native admissions to mine hospitals was made. In only 1 case was the diagnosis of urinary calculi made in this group of patients.

Dr. Vermooten examined personally the records of the Johannesburg General Hospital covering the years from 1922 to 1935 inclusive. Of 91,000 colored patients, only four had urinary calculi. One was an Indian, two were half caste and only one was a full blooded Negro. The diagnosis of the last case was not certain as it was made only by x-ray examination and cystoscopy was refused. His final conclusion was: "The South African Negro (Bantu) does not form renal calculi, as illustrated by examination of the hospital admission records of 1,091,000 Negro patients."

Dodson and Clark pointed out that in their experience in the Hospital Division of the Medical College of Virginia urolithiasis in the Negro in their region is by no means uncommon. Since reports from Africa indicated a freedom from urolithiasis on that continent they believed that American Negroes may have lost in part their immunity to this disease.

OBSERVATIONS IN THE BELGIAN CONGO

Our experience has been limited to the Central Equatorial portion of the Belgian Congo (fig. 1). The Natives are members of the Bantu tribes and are testing or complement fixation studies in possibly infected cases; not only in venereal disease clinics but in hospitals and office practice as well. The reporting of these cases to the local public health groups and the following up of contacts would also prove of great value in controlling a serious and debilitating disease which probably exists in the Kansas area in a much higher incidence than is suspected.

CONCLUSIONS

The acute inguinal form of lymphogranuloma venereum may simulate incarcerated femoral hernia. Two such cases are presented and the differential diagnosis is discussed.

A short résumé of the disease process lymphogranuloma venereum is presented as well as newer concepts of therapy.

Available statistics would indicate that lymphogranuloma venereum exists in Kansas much more commonly than it is suspected or diagnosed, a situation which undoubtedly exists in other areas experiencing a similar influx of those population groups having a high incidence of latent disease.

and moderate edema of the prepuce. There was no urethral discharge but the urine was positive for white blood cells and albumin. Sulfathiazole was given for a period of 1 week to counteract infection of the foreskin, but with only slight improvement. An attempt was made to introduce a small metal sound when a stone was encountered at the external urethral orifice.

On October 29, 1946 a circumcision was performed together with the removal of a small jagged oblong shaped calculus from the urethral meatus. No further investigation of the urinary tract was made at that time.

Three months later the patient returned with the same symptoms as those from which he had suffered prior to operation. A metal sound was passed and a calculus felt within the urinary bladder. On February 3, 1947 a suprapubic cystotomy was performed and a stone the size of an English walnut removed. He was discharged 2 months after operation completely symptom free.

TREATMENT AND RESULTS

All of these cases were treated surgically with removal of the stones through a suprapubic incision. In all cases a self-retaining urethral catheter was inserted. In several cases in which there was marked purulent cystitis, a suprapubic rubber tube was placed in the bladder to use for irrigation.

In the series of 18 patients, ten were checked at variable periods from 2 months to 18 months after surgery. All of these cases were symptom free. Another patient who did not present for examination was reported to be symptom free. However one of these patients had a urethral discharge which ceased following treatment with sulfathiazole. A second case in this group of ten was examined 16 months after operation and had no symptoms, but scattered white blood cells and albumin were found on examination of the urine. He was given penicillin for 3 days then left the hospital without further check-up.

Two patients died one and two weeks respectively after operation. Both had markedly hypertrophied prostate glands that were enucleated at operation. Both had marked purulent cystitis at the time of surgery. A third patient who went home against our advice died on the way to his village. Another patient was reported to have died at home but the cause of death was not determined. Those who died were the four oldest patients of the series. The mortality rate for patients with bladder stones was much higher than the mortality rate for all of the major surgical cases combined. The average for the latter was 2.5 per cent. Three remaining cases had no postoperative check-ups after discharge from the hospital.

In the region of Central Congo where we work, the natives are extremely primitive. The food supply does not meet the demand although actual starvation is not the rule. The chief source of food is manioc, which is a starchy tuber with a high fiber content. Leaves from this same plant are used for greens when cooked in palm oil. Another source of vegetable food is young shoots of a forest plant that is very prevalent in the area.

Meat and fish are scarce. Forest animals are the chief source of meat but these are difficult to kill because of the thick jungle growth and the primitive methods very primitive. This report deals with cases admitted during a period of two years from July 1946, to July 1948. During this 2-year period 18 patients with calculi of the urinary bladder were treated by operation. The accompanying photograph shows this collection of calculi (fig. 2).

During this same period a total of 403 major operations were performed. Thus of all major operations during this 2-year period 4.46 per cent were for bladder stones. The total number of admissions to the hospital and dispensary during this period was about 8,000 patients.

In this group of 18 patients, twelve were males and six were females. The ages of the patients were estimated in all cases as there are no birth records in this area. The youngest estimated age was 4 years and the oldest was 63 years. The average estimated age was 35 years. The average weight of this group of patients was 79.2 pounds.

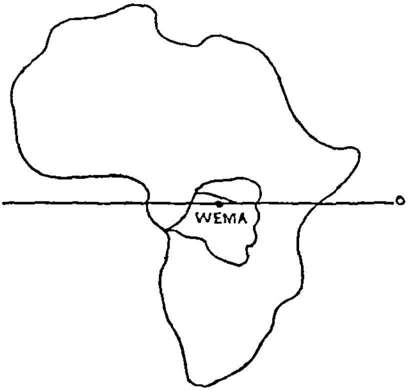

FIG. 1

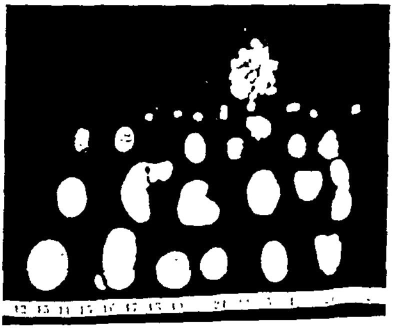

FIG. 2

FIG. 1. Location of Wema Hospital Belgian Congo, Africa

FIG. 2. Urinary bladder stones removed during a 2-year period, 1946 to 1948. Scale in inches.

As to symptomatology practically all of these patients stated that they were suffering from "lisafu." This is the native name ordinarily used for gonorrhea. However it also may be used in the description of any disorder of the external genitalia or lower urinary tract by both males and females. Further questioning, usually with difficulty, revealed a history of pain in the bladder region, frequency and marked dysuria.

The diagnosis was made in all cases by exploration of the bladder with metal sounds. No x-ray facilities were available. Probably in many cases of urinary lithiasis the diagnosis was not made because of lack of facilities. This is especially true for renal calculi which cannot be diagnosed readily without the x-ray. A case at point was that of a native patient who died of terminal bronchopneumonia. At necropsy bilateral renal calculi were found.

CASE REPORT

A native boy 4 years of age was first admitted in October 1946, with the chief complaint of pain on urination. There was a marked phimosis with posthitis

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ENTEROCOCCAL ENDOCARDITIS AS A COMPLICATION OF UROLOGIC INSTRUMENTATION

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The high incidence of bacteremia and the possible development of bacterial endocarditis following tooth extraction and tonsillectomy are so well substantiated as to require little comment. It has become standard practice to administer penicillin as a prophylactic measure in an endeavor to protect against such complications.

Less widely publicized is the incidence of bacteremia following urologic procedures. Creevy and Feeney[1] found bacteremia in 45 per cent of patients undergoing transurethral resection. Powers[2] was able to culture bacteria from the blood of 10 per cent of patients subjected to urethral instrumentation. This is not surprising in view of the high incidence of bacteriuria in patients requiring urologic procedures. More recently reports have appeared demonstrating the relationship between urologic procedures and subacute bacterial endocarditis.[3, 4, 5]

Although any organism associated with genito-urinary infection may produce a bacteremia, the organisms most commonly responsible for endocarditis following genito-urinary surgery are the enterococcus (Streptococcus faecalis) and Staphylococcus aureus. These organisms are often penicillin-resistant. Thus the management of patients with endocarditis caused by these organisms is usually difficult.

We have had occasion to observe 4 cases of subacute bacterial endocarditis due to the enterococcus.* In all the infection developed following urologic procedures. One is of particular interest in that the infection developed in the hospital despite the administration of doses of penicillin and streptomycin usually considered adequate in the prophylaxis against postoperative infection.

CLINICAL MATERIAL

The four cases presented were all hospitalized and studied at the New England Center Hospital.

The pertinent information concerning the antibiotic employed, dosage, duration of treatment as well as the results are summarized in table 1. The diagnosis was suggested by the presence of obscure fever, cardiac murmurs, embolic

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Read at a meeting of the New England Cardiovascular Society, May 21, 1951.

The aureomycin used in this study was supplied through the courtesy of Dr. Benjamin Carey, Director of Clinical Research, Lederle Laboratories Division, American Cyanamid Company.

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* The summary of therapy in three of these cases has been previously reported: Kane and Finn: New Eng. J. Med., 244: 623, 1951.

of hunting that are used. Fish also are obtained with the use of primitive methods. All of these foods are highly seasoned with red peppers. Cereal grains and beans are not widely used in our area.

Drinking water is obtained from springs. It is carried from the springs in gourds by the women and girls of the villages. It is the natural tendency to conserve water and only sufficient quantities are used to quench thirst. It is a native custom to taboo water when one is ill. This theory is encouraged by the witch doctor. Also a woman who is pregnant drinks the least amount of water possible on the theory that she does not wish to drown the fetus. During labor she will not drink any water on her own volition. Dehydration caused by a self or witch doctor imposed low intake of water is often found in patients with pneumonia or other serious illnesses.

These living habits are pointed out as an observation only, because we have no proof that they have any bearing on the etiology of urinary calculi in the Belgian Congo.

SUMMARY

Contrary to the belief generally held that the Negro is immune to urinary calculi, our experience in the central Equatorial region of the Belgian Congo has shown that this is a common disease in our area.

Among 403 patients treated with major surgical conditions during a 2-year period 18 or 4.46 per cent were cases of urinary bladder calculi. The total number of hospital and dispensary admissions during the same period was 8,000. One patient in 444 admissions suffered from bladder stones.

The incidence of urinary lithiasis will probably be found to be even greater than we have observed when more facilities for making an accurate diagnosis become available.

Belgian Congo, Africa

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phenomena, splenomegaly or anemia and was established by repeatedly positive blood cultures.

The "in vitro" sensitivity of the infecting organism was determined against a number of antibiotics including penicillin, streptomycin, aureomycin, chloromycetin, terramycin and neomycin. The results of the sensitivity studies are summarized in table 2. The "in vitro" inhibition levels of the various antibiotics as well as the blood levels when done were determined by the serial tube dilution method described by Rammelkamp.[6] Streptococcus 98 served as the control organism in the determination of levels of penicillin, aureomycin, terramycin, chloromycetin, and neomycin while Bacillus circulans was used for streptomycin.

SUMMARY OF CASES

Case 1. R. K., a 65 year old white man, entered the New England Center Hospital on November 27, 1949. Past history revealed rheumatic fever at the age of 18 years with one recurrence at the age of 23. The presence of a cardiac murmur had been known for about 4 years prior to admission. Ten months prior to admission a urethral dilatation was performed because of urinary frequency. Over the 8 to 10 months period prior to admission, frequent chilly sensations without fever were noted. Four months preceding admission, dyspnea on exertion, as well as paroxysmal nocturnal dyspnea developed and became progressively worse. A weight loss of 45 pounds during this period may have been due in part to a low caloric diet. On admission to the hospital the temperature was 98.6F, pulse 74, respirations 18 and blood pressure 105/50. During the examination the patient experienced frequent coughing spells with resultant dyspnea. Rales could be heard at both lung bases. The heart was enlarged to the left, and a grade 3 loud blowing systolic murmur as well as a rumbling diastolic murmur could be heard over the mitral area. The liver edge could be palpated three fingers-breadth below the right costal margin, and the spleen edge could be felt 2 fingers-breadth below the left costal margin. Pitting edema of both lower legs was present from the ankles to the knees. Roentgenographic and fluoroscopic examination of the chest revealed definite enlargement of the left auricle with evidence of calcification in the region of the mitral valve, straightening of the left border of the heart and prominence of both pulmonary arteries.

TABLE 2. *Minimal concentration of various antibiotics that completely inhibited the growth of the causative organism in 4 cases of enterococcal endocarditis*

Minimal Inhibiting Concentration (after 48 hours)

CASE NO.	PENICILLIN G UNITS/ML.	STREPTOMYCIN MICROGM./ML.	CHLOROMYCETIN MICROGM./ML.	AUREOMYCIN* MICROGM./ML.	NEOMYCIN MICROGM./ML.	TERRAMYCIN* MICROGM./ML.
1	2.5	1.67	6.26	2.5	—	—
2	5.0	2.5	10.0	0.625	3.12	0.78
3	5.0	50.0	6.25	0.313	25.0	0.78
4	6.25	12.5	>20.0	0.625	25.0	0.78

* Twenty-four-hour readings.

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[6] Rammelkamp, C. H.: Proc. Soc. Exper. Bio. and Med., 51: 95, 1942.

CASE NO.	AGE AND SEX	DURATION OF ILLNESS	Antibiotic*	Daily Dosage†	Duration in Days	Results‡	REMARKS
1§	55 M	4 mos.	Aureomycin	4 gm.	8	Failure	Blood cultures remained positive until penicillin in dosage of 12 million units daily was added. Patient died in congestive failure 37 days after therapy stopped
			Aureomycin plus penicillin	4 gm. 2 million u.	2	Failure	
			Aureomycin plus penicillin	4 gm. 12 million u.	17	Cure	
			Penicillin	12 million u.	14		
2§	64 M	8 mos.	Penicillin	8 million u.	30	Failure	Patient remained afebrile but died in congestive failure 60 days after antibiotic therapy was stopped
			Aureomycin	4 gm.	14	Failure	
			Penicillin plus caronamide	8 million u. 24 gm.	42	Cure	
3§	49 M	1 yr.	Aureomycin	2–4 gm.	8	Failure	After 7th day of aureomycin therapy A. aerogenes could be cultured consistently from the blood. Patient died
			Streptomycin	0.5–2 gm.	3	Failure	
			Streptomycin plus penicillin	3 gm. 800,000 u.	5	Failure	
4	52 M	1 wk.	Penicillin plus streptomycin	300,000 u. 1 gm.	6	Failure	Caronamide was given from the 12th to 26th day of combined penicillin-streptomycin therapy because of recurrent lowgrade fever (although blood cultures were negative). Patient remains well 6 months after discharge from the hospital
			Penicillin plus chloromycetin	1.2–3.0 million u. 1.5 gm.	4	Failure	
			Penicillin plus streptomycin	12 million u. 2–3 gm.	32	Cure	

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* The antibiotics are listed according to the sequence of their administration.

† Penicillin and streptomycin were administered intramuscularly; aureomycin and chloromycetin were given orally.

‡ Patients were classified as cured when all evidence of endocarditis, such as positive blood cultures, fever and elevated sedimentation rate were absent.

§ Cases 1, 2 and 3

there was a grade 4 apical systolic murmur heard over the entire precordium but maximal at the apex. No diastolic murmur could be heard. The spleen was palpable one fingers-breadth below the costal margin on the left. The hemoglobin concentration was 8.5 gm. per cent, erythrocytes 3.1 million, leukocytes 9.4 thousand with normal differential. Urinalysis revealed a specific gravity of 1.015, a heavy trace of albumin, no sugar, many erythrocytes and leukocytes. No urine culture was done. Blood cultures on admission revealed a green enterococcus. The sensitivities of this organism to various antibiotics are listed in table 2. On the second hospital day small petechiae were noted in the left conjunctiva. The patient was started on one million units of penicillin intramuscularly every 3 hours and was maintained on this dose 30 days. At the end of this time penicillin was discontinued and 8 days later the patient again had positive blood cultures. At this time he was started on aureomycin, 1 gm. every 6 hours. The temperature returned to normal, but blood cultures remained positive during the 10 day treatment with aureomycin alone. Aureomycin therapy was stopped and one million units of penicillin intramuscularly plus 3 gm. caronamide by mouth every 3 hours was then given. This regimen was maintained for 6 weeks at the end of which time the patient was discharged from the hospital. During the course of caronamide and penicillin therapy he became afebrile and blood cultures were negative. The cardiac murmur became harsher, and congestive failure slowly developed for which he was digitalized. He died at home in congestive failure approximately 2 months after discharge. Permission for necropsy was not obtained.

Case 8. F. C., a 49 year old man, stated that at the age of 20 he was struck on the penis and this was followed by hematuria. Thereafter instrumentation was required every 6 to 8 months in order to keep the urethra patent. There was no past history of rheumatic fever, but at the age of 23 years he was refused life insurance because of a cardiac murmur. In September 1948, he noticed difficulty in urinating and passed a renal stone. Soon afterwards he was admitted to a hospital for urinary difficulty and instrumentation was performed for the removal of several stones. During the hospital stay of 6 weeks he had chills and fever for which penicillin therapy was given. In March 1949, the fever and chills returned and he was again hospitalized. At that time he was treated with streptomycin with a return of the temperature to normal. Chills and fever recurred in July 1949, at which time he was treated with aureomycin. Since that time whenever fever returned he would take aureomycin for a few days and the fever would subside. Blood cultures were taken on several occasions and revealed a gram positive organism which was interpreted as being Staphylococcus aureus. Because of recurrent chills and fever he was admitted to the New England Center Hospital on October 8, 1949. The temperature was 100.2F, pulse rate 92, respiration rate 25 and blood pressure 100/60. Physical examination on entry revealed marked dyspnea and orthopnea and cyanosis of the lips, slight clubbing of the fingers and a small splinter hemorrhage under the nail of the left fifth finger. A harsh, high-pitched systolic murmur was heard in the aortic area, and accen-

There was a slight increase in the prominence of the vascular shadows throughout both lung fields.

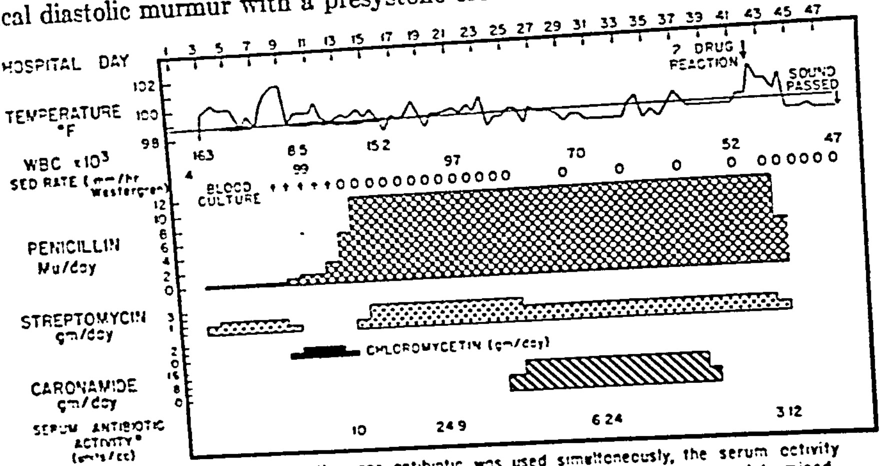
The hemoglobin concentration was 10.2 gm. per cent and leukocytes 9.6 thousand per cu. mm. with 76 per cent polymorphonuclears. The sedimentation rate was 66 mm. per hour (Westergren). Urinalysis revealed a specific gravity of 1.013, 1 to 3 erythrocytes and 8 to 10 leukocytes per high power field, no albumin, sugar or casts. Urine culture showed no growth. Multiple blood cultures taken on admission revealed an enterococcus. The sensitivities of this organism to various antibiotics are listed in table 2.

The patient was started on 4 gm. aureomycin daily by mouth but blood cultures remained positive eight days after this therapy was begun. Penicillin in doses of 2,000,000 units daily in divided doses intramuscularly was then added in addition to the aureomycin, but blood cultures still remained positive. Accordingly the penicillin was increased to 12,000,000 units daily and blood cultures were sterile from then on. The patient received 12,000,000 units of penicillin daily for 31 days. During the last 14 days of therapy only penicillin was given. During the latter period determinations of the serum levels of penicillin showed a value of 20 units per cc 1 hour after an intramuscular injection of 1 million units. At no time was the patient febrile. He died at home in congestive failure 37 days after therapy was stopped. Permission for necropsy was not obtained.

Case 2. C. D., a 64 year old white man, was admitted to the New England Center Hospital on January 16, 1949. He stated he had been well until 1 year prior to admission when on a routine physical check-up "anemia" was found. Eight months prior to admission he was in bed for one week with an illness described as "virus X." He does not recall the symptoms he had at that time, but does recall that during that period a urinalysis allegedly showed hematuria. Six months before admission he was admitted to another hospital because of hematuria, at which time cystoscopy was performed and later prostatectomy. He remained in the hospital 2 months and had no urinary symptoms. After discharge he had urethral dilatations once a week at first and then every 2 weeks. Two and one-half months prior to admission to the New England Center Hospital he became very weak and began to lose weight. Five weeks before admission he had and episode of "pleurisy" with pain in the right axilla on deep inspiration and a temperature elevation to 102F. Also during the 2½ months prior to admission he noticed swelling in the interphalangeal joints and also of the palm of the right hand. The joints were very tender but not red. He gave a history of tooth extraction 2½ months prior to admission. There was no definite past history of rheumatic fever. He had had mild exertional dyspnea for some time and he also had ankle edema prior to the prostatectomy six months before admission.

On admission to the New England Center Hospital the temperature was 97.4F, pulse 80, respirations 16, blood pressure 120/70. There were no petechiae. The chest was emphysematous, but no rales were heard. The left border of cardiac dullness was at the anterior axillary line in the fifth interspace. The apical impulse was heaving; but no thrills were felt. Auricular fibrillation was present and in figure 1. He was known to have a cardiac murmur. Aside from some slight exertional dyspnea he had no symptoms referable to heart or chest and had been completely afebrile. Six weeks prior to admission he noted the sudden onset of urgency of urination. Retention was noted for several hours and then dribbling. Finally he was able to empty his bladder. Since that time he had noted slight burning on urination as well as hesitancy with gradually diminishing size and force of the urinary stream. Two days prior to admission he had a similar episode of marked urgency and inability to void.

On admission to the hospital the temperature was 98F, pulse 70, blood pressure 130/80. The patient had a grade 2 blowing apical systolic murmur and rumbling apical diastolic murmur with a presystolic crescendo. The rhythm was regular.



* Since more than one antibiotic was used simultaneously, the serum activity represents the total activity of the combination. Levels were determined on serum samples drawn 1 hour after a penicillin injection.

FIG. 1

The prostate showed a grade 2–3 enlargement with slight asymmetry. The hemoglobin was 12.8 gm. per cent, erythrocytes 4.0 million per cu. mm., leukocytes 16.3 thousands with 8.1 per cent polymorphonuclears. Sedimentation rate (Westergren) was 4 mm. per hour. Urinalysis revealed specific gravity of 1.025, very rare erythrocytes, no leukocytes, casts, albumin or sugar. Urine cultures were not done. Excretory urography showed bladder changes consistent with intravesical prostatic hypertrophy. On the second hospital day, under pentothal and spinal anesthesia, a suprapubic prostatectomy was performed. Postoperatively the patient was placed on 300,000 units of aqueous procaine penicillin and 1 gm. of streptomycin intramuscularly daily. Although the patient had been afebrile for the 2 days prior to operation, his temperature rose to 100F postoperatively, and remained elevated. On the fifth postoperative day he experienced a chilly sensation lasting a few minutes. Blood culture at that time showed an enterococcus. The in vitro sensitivities of the organism to various antibiotics are shown in table 2. On October 23, he was given 100,000 units of aqueous penicillin G intramuscularly hours. On that date streptomycin was discontinued and chloromycetin 250 mg. every 4 hours was given by mouth. On October 25, penituation of the first sound at the apex. The tip of the spleen could be felt on deep inspiration. The urine showed a specific gravity of 1.010, a faint trace of albumin, occasional red blood cells, 20–25 white cells per high power field and many bacteria. Culture of the urine revealed Proteus vulgaris initially, and later both Proteus vulgaris and enterococcus. The hemoglobin concentration was 8.5 gm. per cent, erythrocytes 2.8 million per cu. mm. and leukocytes 8.5 thousand per cu. mm. with a definite shift to the left. The sedimentation rate (Westergren) was 141 mm. per hour. Urinalysis revealed a specific gravity of 1.015, many leukocytes, 2–4 erythrocytes, large trace of albumin and no sugar. Fluoroscopic examination of the chest showed no evidence of enlargement of any of the chambers of the heart. On the second hospital day the patient had a shaking chill followed by a rise in temperature. Blood cultures taken at that time were positive for Streptococcus faecalis. The in vitro sensitivities of this organism to various antibiotics are shown in table 2. Thereafter, on seven separate occasions positive blood cultures were obtained. At no time during the patient's hospital stay did he have a negative blood culture. Because the organism was found to be most sensitive in vitro to aureomycin, this drug in doses of 1 gm. by mouth every 6 hours was given. He tolerated the medication fairly well except for periodic epigastric discomfort and nausea. It was believed by the urological staff that the bacteremia was due to the infected bladder and that catheter drainage was necessary. On cystoscopy a urethral stricture was encountered. Through the cystoscope an inflamed bladder could be seen. Retrograde pyelography was not performed because of the fear of retrograde infection. An indwelling Foley catheter was left in place for intermittent irrigation. The presence of the indwelling catheter was complicated by the fact that manipulation of the catheter was followed by a shaking chill and high fever. During this period, in addition to enterococcus, Aerobacter aerogenes could be cultured from the blood. The latter organism was found to be sensitive in vitro only to streptomycin. Accordingly, aureomycin was discontinued and streptomycin was given in doses of 0.5 gm. intramuscularly every 6 hours and later 0.75 gm. intramuscularly every 6 hours. On October 24, 1949, sixteen days after admission and eight days after the start of aureomycin therapy, the patient suddenly lapsed into shock accompanied by a grossly irregular pulse. A diagnosis of mesenteric thrombosis was entertained. The patient remained in a shock-like state and this was followed by transient cardiac irregularity, congestive heart failure, increasing azotemia and electrolyte imbalance. The patient died on October 29, 1949. Postmortem examination revealed rheumatic involvement of the tricuspid, aortic and mitral valves, subacute bacterial endocarditis involving the mitral valve, moderate congestion of the lungs, severe focal embolic glomerulonephritis, hemorrhagic cystitis, retrovesical abscess and localized peritonitis due to ulceration of a portion of the ileum.

Case 4. A. K., a 52-year old white man, entered the New England Center Hospital on October 14, 1950. He gave a history of three attacks of rheumatic fever at the age of 14, 15 and 25 years. The clinical course is graphically illustrated fatally. Such infections are more serious than those due to the Streptococcus viridans. Treatment with streptomycin alone has met with little success.[7, 8] In certain instances a favorable outcome has been effected by the use of massive doses of penicillin [9,10,11,12] with or without supplementary caronamide therapy. In others it has been necessary to resort to combined penicillin and streptomycin therapy.[5, 13] One report of a favorable outcome with combined bacitracin and penicillin therapy is recorded.[14]

Since the enterococcus may be highly resistant to penicillin, the dose of penicillin usually administered to prevent postoperative infections may be inadequate. This is borne out in case 4, in which subacute bacterial endocarditis developed despite the daily administration of 300,000 units of procaine penicillin and 1 gm. streptomycin. Since the enterococcus is rarely sensitive to less than 1 unit of penicillin per cc[15] it seems logical to recommend that at least 10 million units of penicillin and 2 gm. of streptomycin be administered daily. Such a total daily dosage of penicillin by the constant intramuscular drip will give average serum levels of 6.6 units of penicillin per cc.[16] Considerably higher peak levels may be obtained when the same amount of penicillin is given by the intermittent intramuscular method. Although such large amounts of penicillin given to prevent postoperative endocarditis may seem excessive, the resistance of the enterococcus to penicillin justifies such intensive therapy.

Merritt[5] has recommended the prophylactic use of aureomycin. Since this agent is not highly effective in the treatment of enterococcal endocarditis this proposal is open to question.[11, 17] Chloromycetin and terramycin may not be effective prophylactically for the same reason.

In three of the 4 cases presented, the infection was controlled. In one, despite aureomycin and streptomycin alone and in combination with penicillin, the patient died. The infecting organism was resistant to 2.5 units but inhibited by 5 units of penicillin. One patient was cured only after giving 8 million units of penicillin daily plus caronamide. Another responded to 12 million units of penicillin daily. The third successful case received 12 million units of penicillin plus 2 to 3 gm. streptomycin daily. Supplementary caronamide therapy was given for a 2 week period in the latter case. However, it is doubtful whether caronamide contributed to the successful outcome since the blood cultures were negative before this agent was employed. In addition, it failed to enhance the

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cillin was increased to 500,000 units intramusculary every 4 hours. On October 27, chloromycetin was discontinued and penicillin was increased to 1 million units every 2 hours. On October 28, dihydrostreptomycin, 0.5 gm. intramuscularly every 4 hours, was given in addition to the penicillin. On November 8, 1.5 million units of penicillin was administered every 3 hours, streptomycin 1.2 gm. every 6 hours. In addition, 2 gm. of caronamide was given orally every 3 hours. The caronamide was started because of persistent slight temperature elevations. Blood cultures were positive on October 22, 23, 24, 25, and 26 and were negative from then on. Serum antibiotic activity levels were determined at intervals and are recorded in figure 1. On the forty-second postoperative day (November 25) the patient had a slight shaking chill followed by a temperature rise to 101F. It was noted that innumerable penicillin injections had resulted in hot tender areas in each buttock. Antibiotic and caronamide therapy was discontinued and the patient was given Sitz baths; within 2 days his temperature returned to normal. Blood cultures drawn at the time of the chill and fever were negative. On the day of discharge, a small sound was passed after which his urinary stream was improved and dribbling that had occurred ceased. On the day following discharge from the hospital the patient had a shaking chill and high fever at home but was treated symptomatically; blood culture at that time was negative. He has been seen in follow-up examinations over a six month period following discharge from the hospital and remains well.

DISCUSSION

Four unselected cases of subacute bacterial endocarditis due to the enterococcus are presented. It is of interest that all cases had previous urologic procedures performed. Two cases had been subjected to prostatectomy, one to urethral dilatation and one to removal of a ureteral calculus via cystoscopy. Three of the cases had known valvular heart disease prior to instrumentation. The etiologic organism in all cases was the enterococcus. This organism is a commensal inhabitant of the intestine. Under certain conditions it may produce pyelonephritis. Second to E. coli, it is undoubtedly responsible for more infections of the urinary tract than any other organism. It is commonly associated with obstructive lesions of the urinary tract such as hypertrophied prostate and urethral stricture. Since instrumentation and surgery of the genito-urinary pasages are frequently followed by a transient bacteremia, it is understandable that organisms present in an infected urinary tract may lodge and produce an infection on a previously damaged heart valve. The incidence of such a complication must be very low, since Merritt found only 8 cases of endocarditis as a complication of 7,000 transurethral prostatic resections. How many of the 7,000 patients had valvular heart disease is not stated.

The enterococcus is known to be moderately to highly resistant to penicillin. It is usually more resistant than the Streptococcus viridans which is so often the etiologic organism in subacute bacterial endocarditis. Infections due to the enterococcus frequently pose problems in management and not infrequently end

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HEMATURIA WITH SICKLE CELL DISEASE

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Hematuria presents a challenge to the urologist. This challenge is usually met by discovering the cause of the hematuria. Infrequently, however, the only attainable diagnosis is "idiopathic" or "essential hematuria." With the recognition of sickle cell disease we believe a certain number of cases will no longer be undiagnosed.

Abel and Brown, in 1948, reported the case of a patient with hematuria, thought to be caused by a renal neoplasm, but actually caused by sickle cell anemia.

Goodwin et al. personally observed 4 patients with hematuria and associated sickle cell disease. In their report (1950) they also included 3 similar patients whose records were reviewed by them.

Ryan and Fuller, 1951, reported the case of 1 patient with hematuria and sickle cell disease. A nephrectomy was done and the microscopic evidence was confirmatory.

Among the Presbyterian Hospital records from 1935 to 1951, we found 14 patients with sickle cell disease. Six of these patients had hematuria and were treated by us.

Through the kind permission of Joseph C Birdsall, M.D., three of his cases from the Graduate Hospital of the University of Pennsylvania are also reported.

The following 9 case reports strongly suggest the relationship between hematuria and sickle cell disease.

CASE REPORTS

Case 1. P. H., 123519, a 42 year old Negro, had hematuria for 10 days. Another urologist had made a diagnosis of left renal tumor because of bleeding from the left ureteral orifice and a filling defect on a retrograde pyelogram. The patient was referred to us January 12, 1950 for a left nephrectomy.

The patient was carefully examined and found to have weakness, dizziness, and shortness of breath. His hematuria had continued. He gave no history of anemia. The principal physical finding was a soft systolic heart murmur.

Cystoscopy on January 13, 1950 revealed blood spurting from the left ureteral orifice. Indigo carmine appeared from both ureteral orifices in 5 minutes. The left renal pelvis was lavaged with 1:500 solution of silver nitrate in a futile attempt to stop the bleeding. The retrograde pyelogram was normal.

Cultures and smears from the urine of both kidneys gave no evidence of tubercle bacilli or other bacteria.

Blood chemistry studies were normal. Blood counts were done daily from

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Read [illegible] American Urological Association, Chicago, Ill., May 2[illegible], [illegible] April 7, 1952.

penicillin blood level. Approximately 8 per cent of patients receiving caronamide fail to show any increase in the serum concentration of penicillin.[18]

These cases are illustrative of the massive doses of penicillin which are necessary to effect a successful outcome in the treatment of enterococcal endocarditis. It is of interest that aureomycin failed in all 3 cases in whom it was used.

Evidence both in vitro and in vivo indicate that there is an apparent synergistic action of penicillin and streptomycin against the enterococcus.[19, 20, 21] So clear cut is the evidence that we believe the penicillin-streptomycin combination to be the antibiotic of choice in the treatment and prophylaxis of enterococcal endocarditis. This is of interest since the enterococcus is usually resistant to streptomycin alone.

Despite the bacteriologic cure effected in three cases, two subsequently died in congestive failure. The poor prognosis of patients with subacute bacterial endocarditis manifesting congestive failure before or during antibiotic therapy has been amply demonstrated.[22, 23] The successful outcome of case 4 was probably due in part to the early recognition of the disease, the prompt isolation and identification of the etiologic agent and early institution of appropriate and adequate antibiotic therapy.

CONCLUSIONS

Urologic procedures especially in the presence of pre-existing valvular heart disease may be responsible for subacute bacterial endocarditis.

The endocarditis thus produced may be due to the enterococcus, an organism which is likely to be highly resistant to penicillin. Despite the high resistance of the enterococcus to penicillin, subacute bacterial endocarditis caused by this organism may be cured by penicillin given in large amounts.

Although in vitro sensitivity tests were favorable, aureomycin proved ineffective in three cases of enterococcal endocarditis treated with this agent.

Although massive amounts of penicillin alone may effect a cure, in vitro tests and a limited number of clinical trials indicate that combined penicillin and streptomycin administration is the therapy of choice in enterococcal endocarditis. Treatment with at least 8 to 12 million units of crystalline penicillin G and 2 grams of streptomycin daily for five weeks is recommended. Similar antibiotic therapy is recommended for patients with valvular heart disease immediately preceding and for several days following urologic procedures.

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tiredness were also noted. Treatment was received at another hospital, but no diagnosis had been made and bleeding continued.

The physical examination revealed nothing abnormal.

Cystoscopy demonstrated bleeding from the left ureteral orifice. Indigo carmine appeared from both ureteral orifices in 3 minutes. The retrograde pyelogram was negative. No tubercle bacilli were found in urine smears, cultures, or guinea pig inoculation. Innumerable red blood cells were found in the urine.

Blood counts varied only slightly from: Hemoglobin 12.6, 81 per cent, red blood cells 4.25, white blood cells 5.7 with normal differentials. The erythrocyte sickling test was positive on two occasions.

The blood chemistry was normal. The Wassermann was 4 plus, but the spinal fluid was normal. Luetic therapy had been given.

Because of the duration and the amount of the bleeding it was decided to do a nephrectomy. The diagnosis was hematuria caused by sicklemia.

A left nephrectomy was easily done February 8, 1950. The pathology report is summarized as follows. Gross description: Tips of several papillae are pitted with 0.1 cm. depressions and occasional purplish discoloration is present in other papillae.

Microscopic description: Capillary bed of kidney is engorged, and in some areas venous sinuses are greatly dilated and distended with blood. There is irregular edema of pyramids, in some linear portions of which it is striking. Blood within vessels shows sickling of virtually all erythrocytes. Diagnosis: Congestion and edema of the kidney; hematuria associated with sicklemia.

No hematuria was noted following operation. He was discharged from the hospital February 23, 1950.

When the patient was seen in the clinic March 17, 1950, the hemoglobin was 97.8 per cent and the red count 5.01 million. There has been no recurrence of hematuria since.

Case 3. P. H. 7292. On February 6, 1950, this 28 year old Negress was admitted to the hospital with the chief complaint of hematuria for 5 days. A year before this she suffered from nausea, anorexia, and epigastric pain with associated jaundice. Recently she had been dizzy and weak, and had aching legs. She admitted to an attack of hematuria 7 years ago. It was recalled that a maternal aunt had anemia.

Cystoscopy revealed blood spurting from the left ureteral orifice. Indigo carmine appeared in 5 minutes from the right ureteral orifice and in 10 minutes from the left. The retrograde pyelogram was normal.

Urine smears and cultures were negative for tubercle bacilli and other bacteria. Guinea pig tests were negative.

Urinalysis showed only innumerable red blood cells.

The blood counts averaged: Hemoglobin 12.0, 82.8 per cent, red blood cells 4.14, white blood cells 5.65 with a normal differential. The positive sickling test indicated the sickling trait. Blood chemistry was normal.

Again a diagnosis of hematuria with sickle cell disease was made. A left nephrectomy was done February 8, 1950.

January 12 to 19. They were all approximately: hemoglobin 8.9 gm., red blood cells 3.43, white blood cells 8.7 with a normal differential. Blood sickling test was positive.

Urinalysis showed only innumerable red blood cells.

Cystoscopy was repeated January 23 and blood was again seen spurting from the left ureteral orifice.

Transfusions were given daily for 5 days, but the red count could not be improved.

Because, at the end of 23 days, the bleeding could not be controlled, it was decided to do a nephrectomy on January 25, 1950. The operation was accomplished with no difficulty.

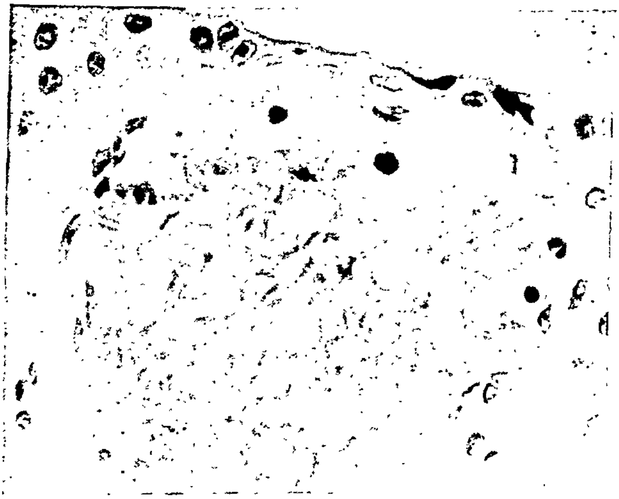

FIG. 1. Dilation and engorgement of submucosal vessel. Note sickling of erythrocytes.

The pathology report is summarized as follows. Gross description: Blood clot noted in pelvis. Papillae of both poles marked by petechiae at or near tip and several papillae are grossly edematous. Parenchyma of medulla has a single 0.5 cm. hemorrhage at one pole and there is perivascular hemorrhage along course of one large straight vein.

Microscopic description: Twenty-five microscopic sections were examined. Renal papillae are markedly edematous and support hugely dilated vascular channels. Scattered small hemorrhages are present in several sectors beneath epithelial lining. Throughout sections, erythrocytes in dilated vessels and in small hemorrhagic areas show sickling in "holly leaf" and crescent shaped forms. Some dilated and engorged vessels are immediately submucosal (fig. 1). Diagnosis: Submucosal hemorrhages of papillae of left kidney; sicklemia.

The patient was discharged February 3, 1950 with no hematuria following operation. He was given liver, iron, and vitamins. On March 9, 1950 his red count was: Hemoglobin 12.3; red blood cells 4.64. He has been well since.

Case 2. P. H. 124038, a 33 year old Negro, was referred to the hospital February 5, 1950 because of painless hematuria of 4 months' duration. Weakness and sickling of the erythrocytes. The blood count was: Hemoglobin 10.8. 76 per cent, red blood cells 4.4, white blood cells 5.0 with a normal differential.

A right nephrectomy was done April 18, 1951. The pathology report follows. Gross description: Calyceal mucosa studded with tiny petechial hemorrhages. Medullary portions of serial section show scattered petechial hemorrhages. Cystic-like areas are noted in pyramids.

Microscopic description: In many sectors there are dilated and engorged vessels and a few small interstitial hemorrhages. Sickling of the erythrocytes is present in the lumina of some of the vessels. One tiny focus of inflammation and necrosis is present in one pyramid. Erythrocytes are present in Bowman's capsule of some glomeruli.

Of interest is a striking hyperplasia of the epithelial lining cells of distal collecting tubules. Some of these foci of epithelial hyperplasia are so extensive as to form solid nests of large columnar cells, while others show cystic dilatation of the lumina, producing the pyramidal cystic changes noted grossly. The change is regarded as hyperplasia rather than neoplasm (fig. 2).

Cases 5 to 9 were not operated upon, but they are all patients with sickle cell disease demonstrating unilateral renal hematuria. For brevity they are merely listed with the principal findings enumerated:

CASE NO.	HOSPITAL NO.	AGE	RACE	SEX	ADMISSION DATE
5	P. H. 88295	26	Negro	Female	6/22/50
6	P. H. 108827	40	Negro	Female	8/10/50
7	G. H. 198264	27	Negro	Male	4/13/50
8	G. H. 183216	14	Negro	Male	3/10/50
9	G. H. 197678	10	Negro	Male	1/22/51

Hematuria had been recurrent in 4 patients, but had previously been undiagnosed. On the present admission 4 had left renal hematuria and 1 had right renal hematuria.

All of these patients had sickling of the erythrocytes, but only one had sickle cell anemia. This patient had a sickle cell crisis under our observation. She was admitted complaining of lower right quadrant pain, nausea, vomiting, dizziness and weakness. This patient had previously been diagnosed as a sicklemic as had one other case.

Bone marrow studies on one patient showed hyperplasia, but studies on two others were normal. The bone x-rays in the hyperplastic case were typical of anemia.

Retrograde pyelography in all cases showed no cause for renal hematuria.

Studies for tuberculosis were negative in the 5 patients.

Hematuria was controlled in all five by the use of whole blood transfusions, raw liver, and vitamins.

DISCUSSION

Sickle cell disease, because of its variety of symptoms and its imitation of other diseases, may be overlooked in differential diagnosis because the physician [illegible] think of it. It is a disease principally of the Negro race, occurring in

The pathology report was as follows: Gross description: Hemorrhagic softening of several papillae is noted. A hemorrhagic area 0.5 cm. in diameter bulges from surface of a papilla in a lower pole pyramid.

Microscopic description: Renal parenchyma is markedly hyperemic. In some sectors there is edema in the renal papillae, and in these areas lining cells of the collecting tubules appear hyperplastic. A few small submucosal hemorrhages are present in renal papillae. Sickling of the erythrocytes is noted within engorged blood vessels. Diagnosis: Hematuria associated with sicklemia.

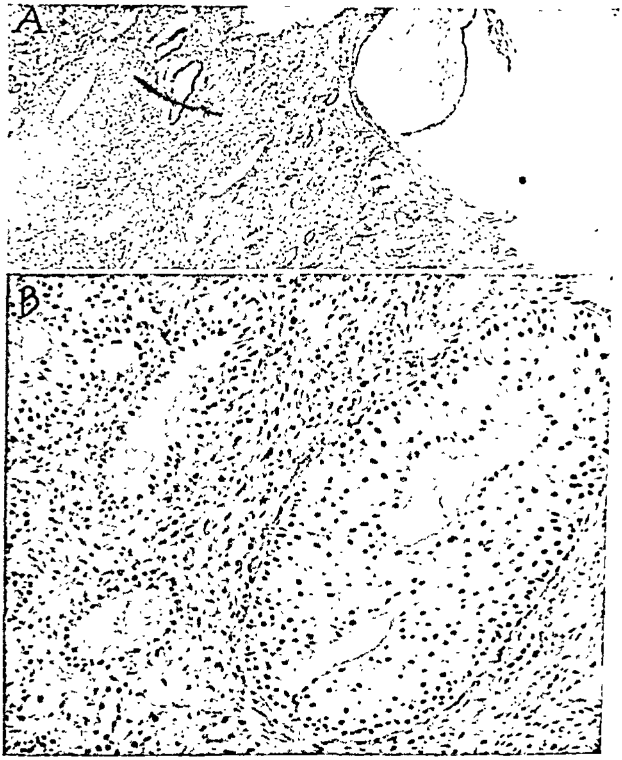

FIG. 2A. Cystic dilatation of distal collecting tubule (right side of picture).
FIG. 2B. Hyperplasia of lining cells of distal collecting tubule.

The patient made an uneventful recovery. No hematuria has since occurred. The red count has remained normal, but 30 per cent sickling of the erythrocytes is noted in one hour.

Case 4. P. H. 133407, a 31 year old Negress, was admitted April 13, 1951 complaining of bloody urine. She thought the blood was coming from excessive menstrual flow, but her family physician catheterized her and found her urine was grossly bloody.

No abnormalities were noted on physical examination.

Blood was seen spurting from the right ureteral orifice at cystoscopy. Indigo carmine appeared from both orifices in 5 minutes. No growth was obtained on urine cultures. There were innumerable red blood cells in the urine. The retrograde pyelogram was normal.

Diagnosis of hematuria with sickle cell disease was made because of the marked gory and otherwise would have been classified as idiopathic hematuria. They are all being followed with special attention to the possible recurrence of hematuria.

When faced with the marked hematuria that the patients in the foregoing case reports suffered, and in contemplating surgery, we wondered if the other kidney might also become the site of similar bleeding, and if not, why not? In searching for the answer some interesting studies were uncovered.

It has been generally assumed that man is a symmetrically developed organism. Certain asymmetries, however, are present in the normal individual. Some of these asymmetries are slight but varying degrees exist. The difference in the two sides of the face is a frequently used example of asymmetry. Gislen has made a study of the lower forms of ilfe and uncovered striking asymmetries. Suffice it to say then, that it is conceivable that defects, vascular or otherwise. may occur in one kidney and not in the other. Also it is known that individuals with sickle cell disease are more likely to have congenital defects. Would it not be possible, with some slight defect plus the abnormality of the erythrocytes, that hematuria might develop in one kidney?

From our observation of these patients it is evident that they withstand surgery well because of the advances in anesthesia and the proper use of transfusions and other supportive measures. We therefore believe that nephrectomy is the treatment of choice in patients with sickle cell disease suffering from massive unilateral renal hematuria.

SUMMARY

Nine patients with unilateral renal hematuria and associated sickle cell disease are reported.

The pathology reports of four kidney specimens from these patients lead us to believe sicklemia to be the cause of hematuria.

The shock or preshock theory of Kimmelstiel explains the process of sickling of the erythrocytes with resultant peripheral vascular spasm leading to ischemic necrosis of tissue by "packing" of the capillaries with sickled cells causing damage to the vessel walls and ultimately infarctions.

Sicklemia associated with some inherent defect found only in one kidney is proposed as an explanation of unilateral renal hematuria.

With modern advances, it is believed that surgery is not contra-indicated in sicklemics; therefore it is our opinion that nephrectomy is indicated for uncontrollable unilateral renal hematuria associated with sickle cell disease.

[illegible] Spruce St., Philadelphia 3, Pa.

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7–8 per cent of American Negroes, but a number of cases have been reported in the white race.

Erythrocytes of sicklemics have the capacity to undergo reversible changes in shape in response to changes in partial pressure of oxygen. With lowered pressure these cells change from the normal biconcave to crescent, holly leaf, and other forms, a process known as sickling. Those individuals who have pathologic consequences with severe chronic anemia are said to have sickle cell anemia. These are 1 in 40. The remainder are said to have sicklemia or sickle cell trait.

The main observable difference between erythrocytes of the two types is the greater reduction in partial pressure of oxygen required for sickling of a major portion of trait cells than for anemia cells.

There has been great controversy over the pathology of sickle cell disease. Kimmelstiel (1948) however, carefully studied case reports and cases under his own observation. From these he theorizes:

"1) Sickle cell crisis constitutes an equivalent to preshock or shock. The crisis may be initiated by various factors which produce a decrease of oxygen in the peripheral blood. It is characterized by rapid blood destruction and an obviously decreasing ability of the erythrocytes to carry oxygen. The mere fact that the erythrocytes are sickled proves that they do not carry sufficient oxygen. In accordance with our present concept, peripheral vascular spasms may at least temporarily maintain normal blood pressure, but it will also produce tissue anoxia, leading to further sickling and to the introduction of a vicious cycle.

"2) The peripheral vascular spasm may lead directly to ischemic necrosis in inner organs or may be followed by capillary dilatation or stasis. During this phase of failure of peripheral circulation the capillaries "are engorged" and "packed" with sickle cells. We regard this phenomenon as a result rather than the cause of capillary stasis.

"3) Local ischemia of tissue and capillary walls may result in organic damage to the vessel walls, degenerative changes, and thrombosis, resulting further in superimposed infarctions."

This theory eliminates the concept of primary capillary blockage which cannot be correlated to gross infarctions without assuming an unrelated process in larger vessels. It explains the frequent reports of ischemic infarctions without vascular thrombosis as well as the occurrence of thrombi.

Medical treatment of this disease has been discouraging. Good nutrition is important along with transfusions, liver, iron, and vitamin therapy. Anticoagulants have been unsuccessful.

In our first patient with massive hematuria and sicklemia a nephrectomy was done as a life-saving procedure. In spite of objection in the past to surgery on sicklemics, we encountered no difficulties. The result was quite encouraging and no further hematuria was occurred.

In view of this experience we did not hesitate so long in the other 3 cases. Nephrectomies were done, hematuria was stopped, rapid recoveries and return to work early were accomplished by all. Follow-up in the urology and hematology clinics has shown no recurrence in the remaining kidney.

We believe that the nonoperative cases all fit into the sickle cell disease cate-

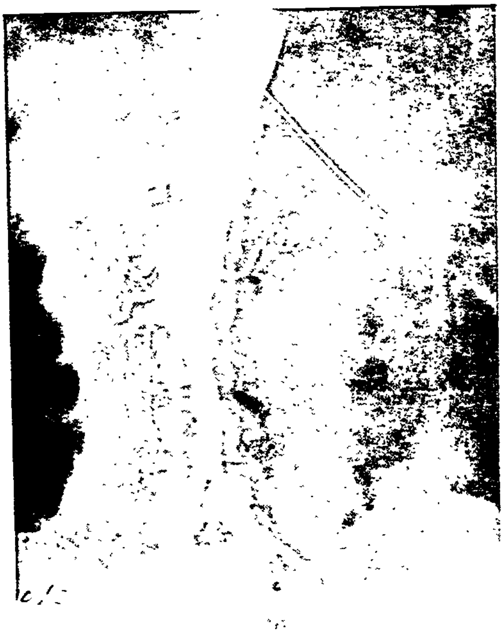

FIG. 2. Aortogram produced after having entered aorta with new 18 gauge needle, injecting 30 cc of 70 per cent urokon in 4 seconds. This demonstrates very poor blood supply to a right kidney involved with atrophic pyelonephritis in a patient suffering moderate hypertension. Normal blood supply to left kidney.

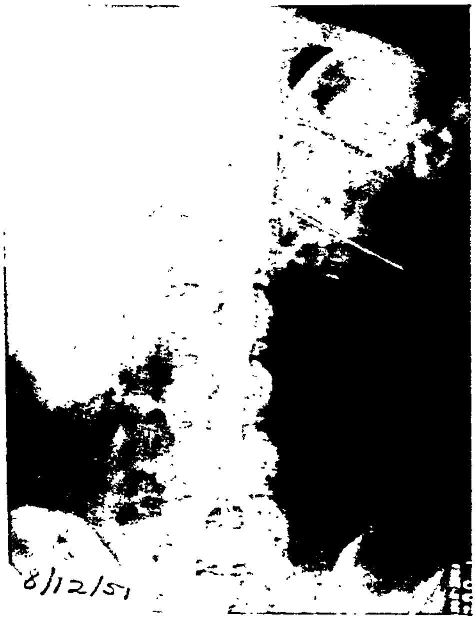

FIG. 3. Same materials and technique as employed in figure 2. Aortogram demonstrates pooling out of medium in large hypernephroma suffering moderate degeneration. (In making print, over-development was used to bring out detail in large right renal mass, thereby lessening distinctiveness in blood supply to normal left kidney.

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RECENT IMPROVEMENTS IN TRANSLUMBAR AORTOGRAPHY

A. KELLER DOSS

Since the introduction of translumbar aortography by dos Santos in 1927, there has been one deterring factor chiefly responsible for disinterest in the procedure, i.e., lack of a suitable radiographic medium for injection. Failure of the pharmaceutical houses to develop a solution of high molecular weight, low viscosity and low toxicity has greatly retarded the progress of aortography.

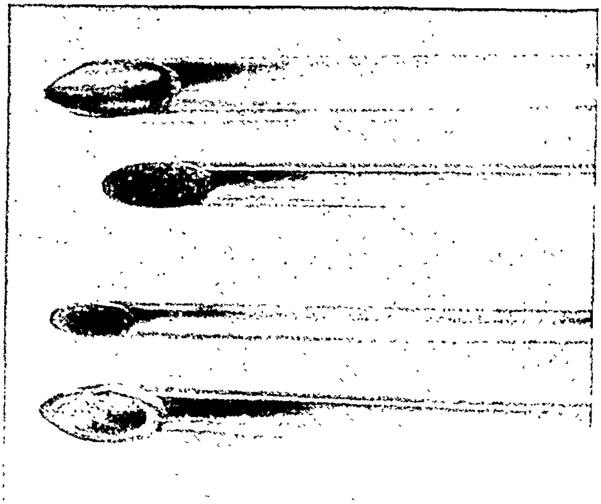

FIG. 1. Shows relative sizes of new and old 18 gauge needles. Upper needle and stillete is that of new thin walled needle, while lower is that of conventional needle ordinarily used.

Until the introduction of 70 per cent Urokon® Sodium by the Mallinckrodt Chemical Works, only 80 per cent sodium iodide solution, in my hands, had proven satisfactory for aortography. Even with this new medium adequate concentration of the solution in the aorta was not sufficient to produce uniformily clear arterial delineation until employing a needle made for me by Oscar Schwidetzky of the Becton, Dickinson and Company. This needle is of a new construction made from thin walled tubing enabling the manufacturer to supply a 17 gauge bore in a needle with outside diameter no larger than 18 gauge (fig. 1). The advantage of this is immediately apparent. The more rapid the delivery of the contrast medium into the aorta, the better concentration, and therefore, the more distinct the arterial outline. Until the "ideal" solution has been produced, the rapid concentration of a volume of the medium in the aorta will necessarily govern the quality of the roentgenogram.

In order to gain satisfactory information from an aortogram the technical quality of the film must be good. Too often effort is made to read into or exclude from the roentgenograms information which is obviously founded on hope or surmise owing to technical inadequacy, wishful radiology. In my travels I am

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EXTRAPERITONEAL PNEUMOGRAPHY

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The retroperitoneum and the structures which it contains have similar densities, hence these organs are seen poorly if at all on plain roentgenograms. Thirty years have passed since Carelli described the technique of perirenal air insufflation which allowed of clear delineation of the kidneys and, often, the adrenal glands. At the present time, however, it is not widely employed because a significant number of deaths from venous (pulmonary) gas embolism have been observed. Most of these may have followed errors in technique since Cahill, one of the few who still use the procedure extensively, has performed more than 600 without observing an alarming reaction. Certainly more prosaic methods of roentgenography fail to demonstrate small adrenal tumors though the presence of larger ones may be implied by displacement of a kidney.

Recently a method of pneumography has been described which is broader in diagnostic scope, yet has proved, so far, to be safe in application. Rivas found that, by introducing a needle into the caudal (sacral) canal and allowing oxygen to flow through it, the retroperitoneal, mediastinal, and cervical soft tissues became emphysematous thus clearly showing the organs in these areas on x-ray films. Later, he found that the gas could be more readily limited to the subdiaphragmatic extraperitoneal area by introducing it in the presacral-retrorectal zone. He chooses to introduce the needle to one side of the sacrococcygeal joint. With the patient lying prone, 1000–1200 cc of oxygen are then allowed to flow into these tissues. Films taken 2 hours later clearly demonstrate the psoas muscles, kidneys, adrenals, liver, spleen, and the leaves of the diaphragm.

Others have followed his technique and have reported enthusiastically on its value as well as the lack of undesirable reactions. DeGennes, May, and Simon introduce the needle in the midline just distal to the coccyx. They also employ 1000–1200 cc of oxygen but introduce it under 300 gm. of pressure thus requiring only 3 minutes for the insufflation.

We have now used this diagnostic procedure in close to 100 patients. This experience has caused us to modify the technique in some respects. After placing the patient on his right side (if the operator is right handed), 1 per cent procaine is injected in the skin about 1–2 cm. below the tip of the coccyx in the midline (fig. 1, *A*) and anesthetic ointment is applied to the anus. A short No. 19 spinal needle has been our choice because it is stiff enough to guide with accuracy. It is inserted through the wheal and passed just anterior to the tip of the coccyx. The index finger of the left hand is then placed in the anus which allows safe and accurate advancement of the needle (fig. 1, *B*). It is made to "hug" the sacrococcygeum to avoid puncturing the rectum. The tip of the needle should finally

Supported in part by the Breon Fund for Medical Research and in part by the American Cancer Society Institutional Grant.
Read at annual meeting, Western Section, Pasadena, Calif., May 19, 1952.

frequently shown roentgenograms which present poor delineation. To render an interpretation of such a film is simply to court disaster. If the study is worth doing, we must insist on good quality. It is this effort to maintain a high standard in aortography which has prompted my continued use of 80 per cent sodium iodide, not withstanding its toxicity, all the while insisting that the pharmaceutical houses busy themselves in developing an "ideal" medium.

Now it appears that 70 per cent Urokon® Sodium, when injected through one of the new needles in quantities up to 30 cc in three to four seconds, will produce an aortogram of sufficient quality as to allow the discard of 80 per cent sodium iodide (figs. 2 and 3). This new medium, introduced by Melick at the meeting of the American Urological Association in 1951,* is the least toxic of all media yet used in arterial visualization. While it does produce some arterial spasm, this too is minimal. Furthermore, its relative radiographic density, per volume, more nearly approaches 80 per cent sodium iodide than media employed to date.

Oscar Schwidetzky is having a 17 gauge needle made which will carry the usual 16 gauge bore. I feel certain that even better results will be accomplished with the use of this needle, however, there is a limit to the size of the puncture one should make in the aorta! He is also having a needle made with a Huber point which will allow one to deflect the medium somewhat. I doubt that this will offer much advantage for it will necessarily slow the speed of injection.

Unquestionably this new equipment, the needle and more especially the medium coupled with rapid cineroentgenography now available, will assist aortography to assume the position it rightfully deserves in the field of diagnosis.

My sincere thanks to Mr. Melvin A. Thorpe of the Mallinckrodt Chemical Works for the 70 per cent Urokon® Sodium so generously supplied for this investigation. I also want to thank Mr. Oscar Schwidetzky of Becton, Dickinson and Company for supplying me with this new thin walled needle.

1611 Medical Arts Bldg., Fort Worth, Texas

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* Melick, W. F., Boler, T. and Byrne, J. W.: J. Urol., 67:1019, 1952.

nes. We first used pressures in the neighborhood of 40 cm. of water but this was gradually lowered to 20 cm. or less, thereby increasing our sense of security. If greater pressures than this are necessary, it is probable that the needle has entered the fascia propria of the rectum or lies in tissue which is fibrous. The position of the needle, in such circumstances, must be changed. We have found that for bilateral retroperitoneal emphysema, 15 cc of oxygen per kilogram is adequate. Unilateral insufflation requires half that amount.

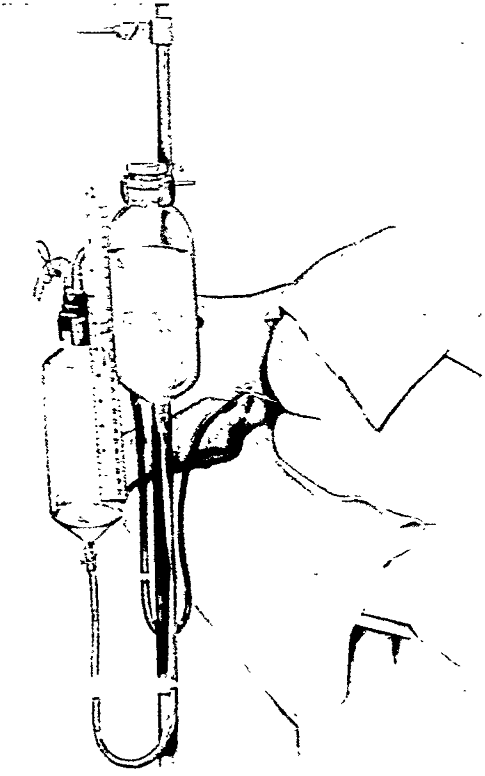

FIG. 2. Apparatus for delivery of oxygen. Lower bottle is filled with water which is displaced to upper bottle by forcing O_2 into the former. Ruler allows of measurement of distances between fluid levels which is the delivery pressure in centimeters of water. Position of bottles must be altered to maintain constant pressure.

After bilateral insufflation, the patient is left prone until the films are taken so that the gas will not spread into the anterior abdominal wall thereby obscuring detail of the retroperitoneum. After injection for unilateral pneumography, the patient is placed in the prone position so the gas can more completely surround the retroperitoneal organs. The head of the table should be raised 15 degrees to encourage the gas to rise to the subdiaphragmatic region which is the area in which we are usually interested (fig. 4).

Roentgenograms are taken at once. If these are not satisfactory, the position of the patient can be altered to facilitate further migration of the gas. Films can then be repeated in 1 or 2 hours. Stereoscopic anteroposterior and lateral films rest about 1 cm. superior to the tip of the coccyx. The needle is then aspirated with a syringe to be sure its point is not in a vessel. The apparatus for delivery of the gas is shown in figure 2. It is attached to the spinal needle by means of sterile tubing in which is a cotton filter.

At first the gas was allowed to flow in with the patient prone but often the oxygen was found to be distributed unequally between the two sides. More accurate placement of the gas is accomplished if one-half the total to be used is introduced with the patient on his side. Then after shifting the patient onto his other side the remainder is allowed to run in. The gas always seeks the highest level. If but one side is to be studied, only that side should be elevated for lateral roentgenograms will be clearer in the absence of gas on the other side (fig. 3).

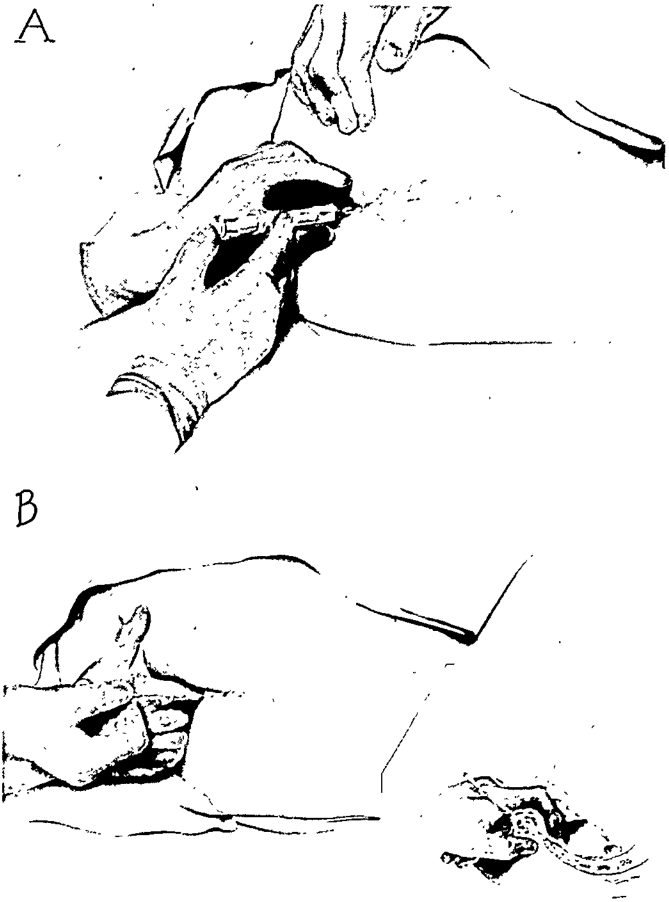

FIG. 1. *A*, placement of needle. Wheal of novocain just caudad to tip of coccyx. *B*, after spinal needle reaches tip of coccyx, finger is inserted in rectum to guide needle in retrorectal zone.

Oxygen appears to be the gas of choice because its solubility is such that good films may be had up to 4 hours after the insufflation. There is also reason to believe that the chance for embolism is minimized. Because of our natural fear of fatal embolism, we were loath to use such high pressures as employed by DeGenuterus, tubes and ovaries. It then dissects upward along the psoas muscles and fills both the perinephric and paranephric spaces thus outlining the kidneys, adrenals, liver, and spleen (fig. 5).

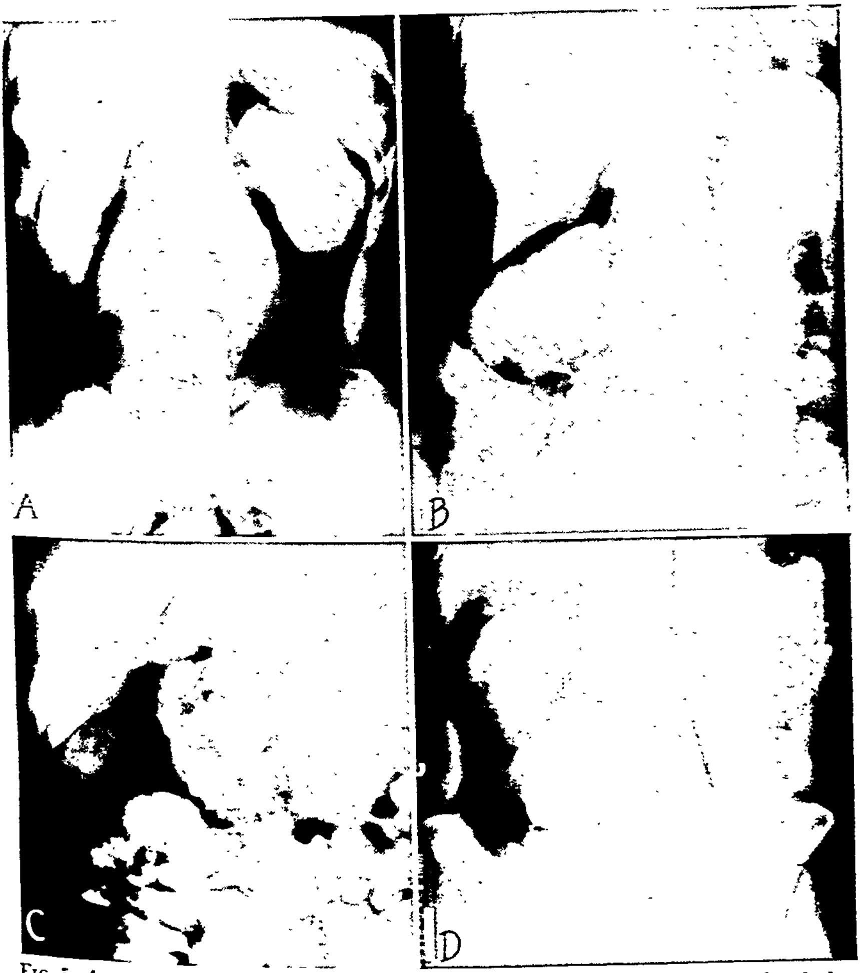

FIG. 5. *A*. normal bilateral pneumogram. Both kidneys and right adrenal gland clearly demonstrated. Left adrenal is questionable. Psoas shadows clear cut. *B*, unilateral pneumogram. Overlying the psoas and opposite L 3 can be seen the dilated pelvis of a hydronephrotic kidney. *C*. unilateral pneumogram. Charcot joint involving L 1–2. Note large soft tissue mass extending from T 11–L 3 with lateral displacement of kidney and adrenal gland. *D*. bilateral pneumogram with intravenous urogram which shows absence of lower calyces on right. Soft tissue mass in lower pole of kidney invading psoas and eroding L 4. Adenocarcinoma of kidney.

Since the only serious complication from this procedure could be venous air embolism it seemed wise to subject animals to the retrorectal infiltration of gas introduced in varying amounts and under various pressures. Pressures of 10, 40, and 160 cm. of water and volumes of 10, 40, and 160 cc of oxygen per kilogram were employed. Dogs were used for these 9 experiments which were accomplished under sodium pentobarbital narcosis (fig. 6). Films were exposed are routine and tomography has been found to be particularly helpful in the elimination of confusing shadows caused by gas in the gastro-intestinal tract.

The technique for producing extraperitoneal emphysema is simple since it is done under local anesthesia, requires only one needle puncture, and excites little discomfort for the patient. As the gas is introduced, it surrounds the rectum and bladder. In the female, it invades the parametrium which envelops the

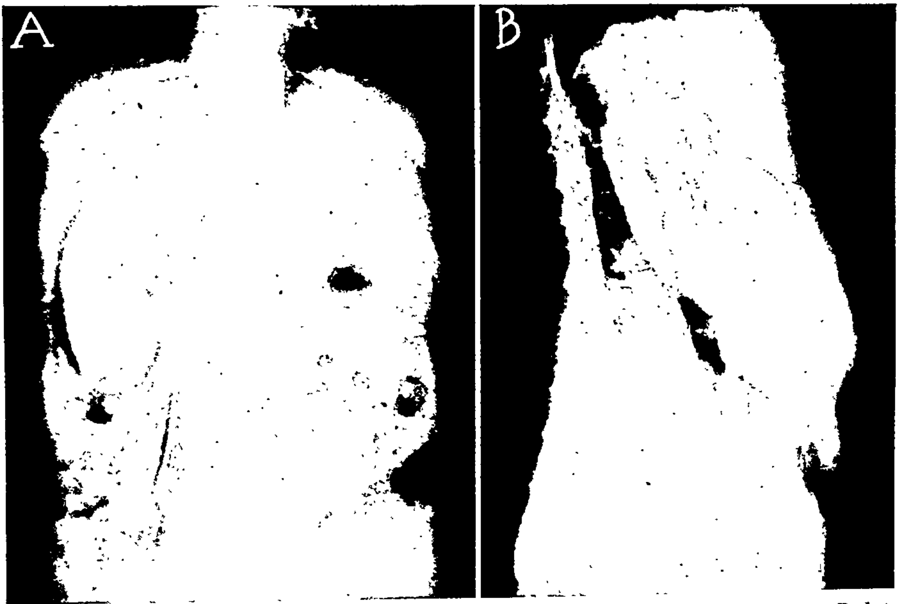

Fig. 3. *A*, normal unilateral pneumogram. Small adrenal gland can be seen. *B*, lateral view of *A*.

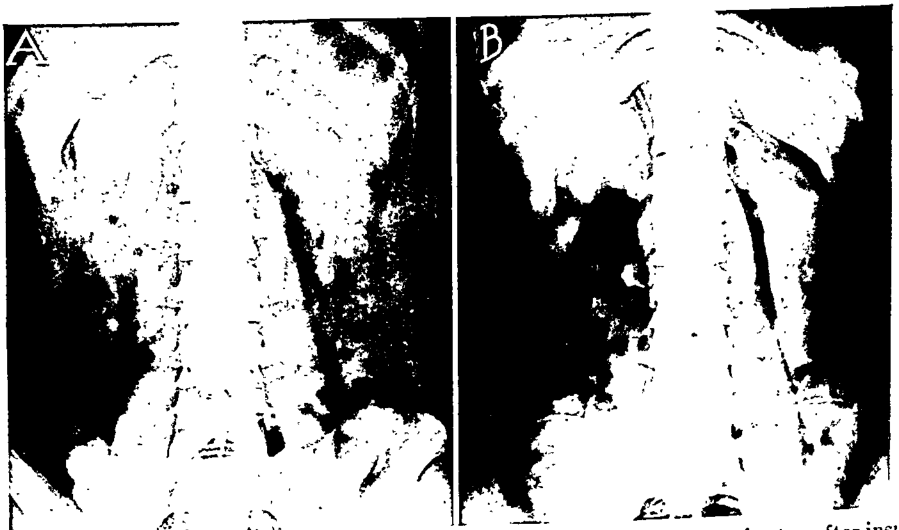

Fig. 4. *A*, bilateral pneumogram—1000 cc of oxygen. Film taken 20 minutes after insufflation. *B*, patient then placed in prone position with head of table elevated 20 degrees. Film taken ½ hour later. This demonstrates how gas can be moved by change of position. Right pheochromocytoma.

lay on its left side, the outflow from the right heart would not become blocked by the gas; the gas was able to leave the heart and reach the lungs. They also demonstrated that if symptoms of embolism developed, placing the animal on its left side usually prevented a fatal outcome.

The signs of venous gas embolus include a "mill-wheel" cardiac murmur often heard without a stethoscope, cyanosis, increased venous pressure, fall in blood pressure, rapid thready pulse, and syncope. If such symptoms develop, the patient should immediately be placed in the left lateral decubitus position. The efficacy of this maneuver has been observed by Hollander and others. The work of Durant only emphasizes the need for careful observation of the patient during the procedure and the importance of the use of low pressures for the introduction of the gas. We believe, if these tenets are not violated, that extraperitoneal pneumography will prove to be a safe procedure as well as a valuable one.

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at 15 minutes, 2 to 3 hours, and 18 hours after insufflation. A few films were taken 6 days later.

It was found that the extraperitoneal tissues have a positive pressure of about 10 cm. of water so pressures a little higher than this were needed in order for the gas to spread into the tissues. Free flow was noted at pressures of 15 to 20 cm. of water. The dogs were not disturbed nor was the quality of the films improved by the use of the higher pressures. More than 10 cc of gas per kilogram seemed to be desirable for good roentgen definition. The introduction of large amounts of oxygen caused no untoward reactions. Roentgenograms taken up to three hours after introduction of the oxygen were good. At 18 hours, about 70 per cent of the gas had been absorbed and at 6 days only a trace remained.

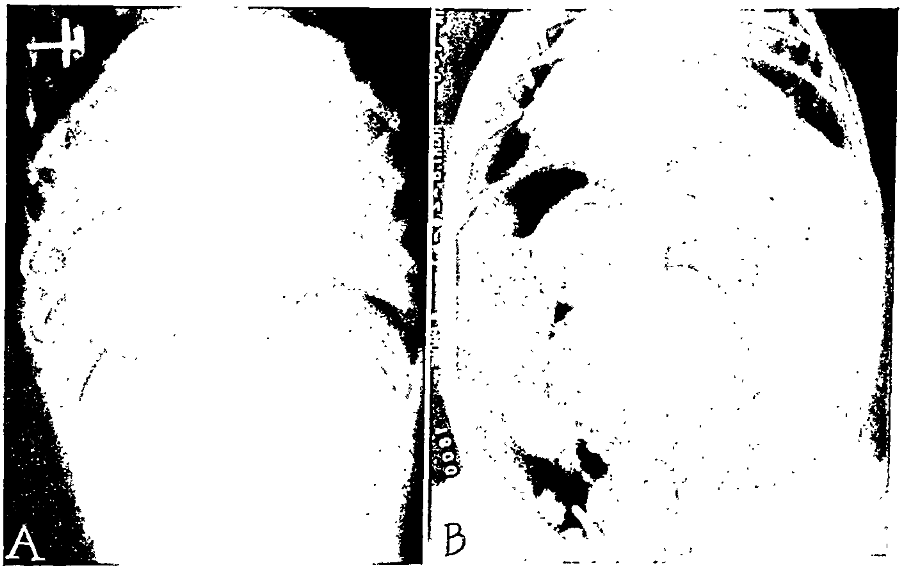

FIG. 6. *A*, dog weighing 14 kg., 40 cc of O_2 per Kg., total 560 cc. Pressure 20 cm. H_2O. Good delineation of kidneys. *B*, dog weighing 10 kg., 160 cc of O_2 per Kg., total 1600 cc. Pressure 160 cm. H_2O. Three lobes of liver on right clearly shown; both kidneys, spleen, diaphragm and loops of bowel demonstrated.

Helium was also used in a series of similar experiments. The dogs did not react adversely to it and the films obtained were no different from those obtained with oxygen. The known insolubility of helium was demonstrated by the fact that after 6 days 80 per cent of the gas still remained in the retroperitoneal tissues. It seemed to offer no advantage over oxygen so it was not used clinically.

There is no doubt of the value of extraperitoneal pneumography. The fear that one must entertain is of gas embolism though no such complication has been cited by those who have reported their experiences with this procedure. Durant, Long and Oppenheimer were able to demonstrate experimentally that the cause of death in venous air embolism is a mechanical blockage of the outflow tracts from the right ventricle by the air. They were further able to show that fatal embolism depended upon the amount of gas injected intravenously, the speed of the injection and the position of the animal. They found that if the animal

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